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The American Journal of Medicine

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BOOK SECTION

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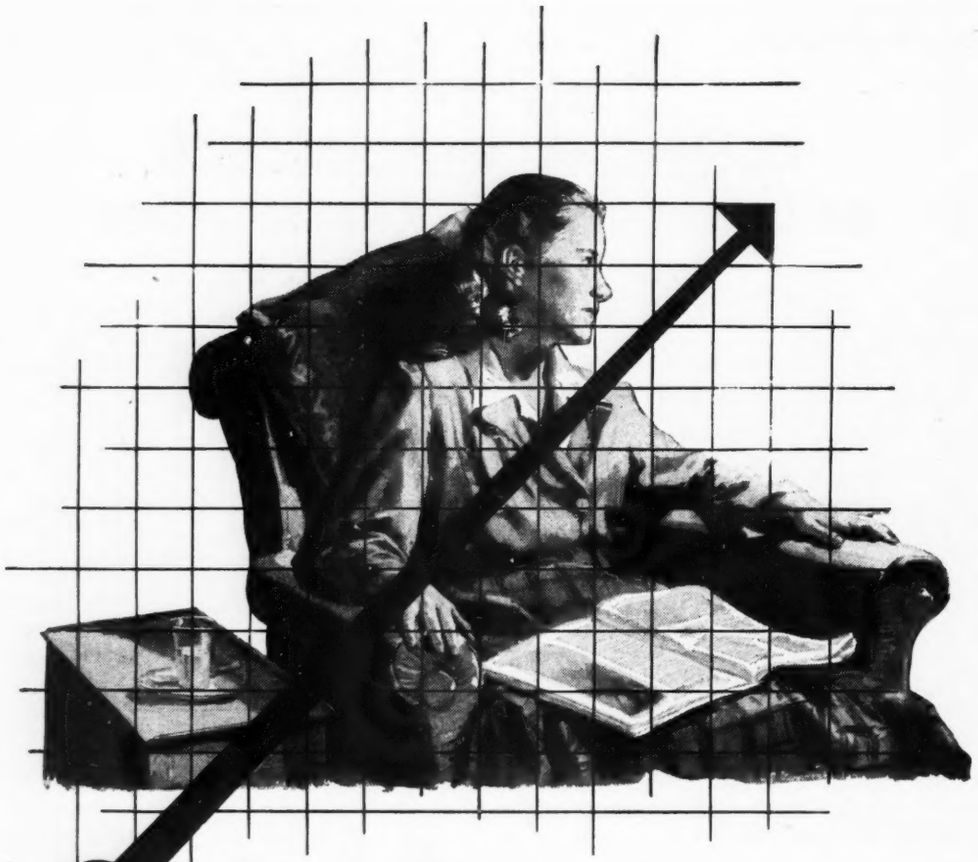

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1. Gordon, E. S.: Nutritional and Vitamin Therapy in General Practice, Year Book Pub., 3rd ed., 1947.
2. Manchester, T. C.: Food Research, 7:304, 1942.
3. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944.
4. Rose, M. S.: Rose's Foundation of Nutrition, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944.
5. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946.

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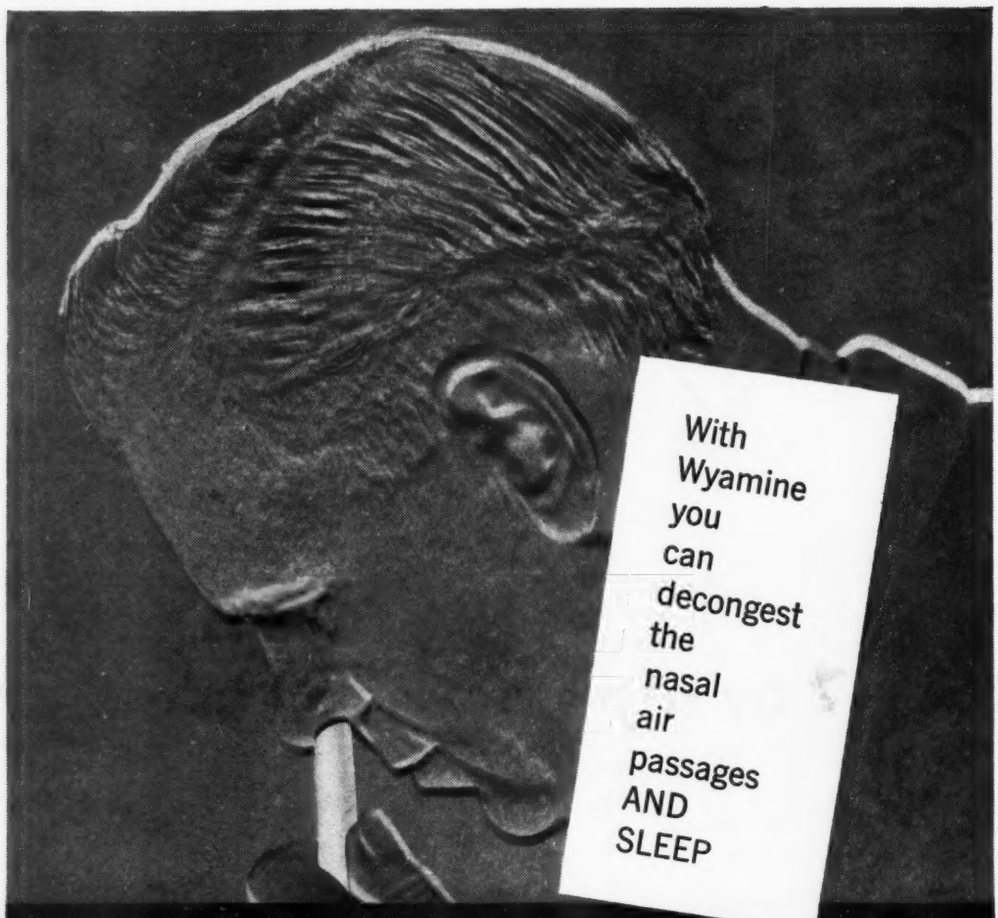

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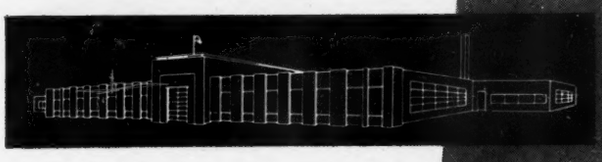

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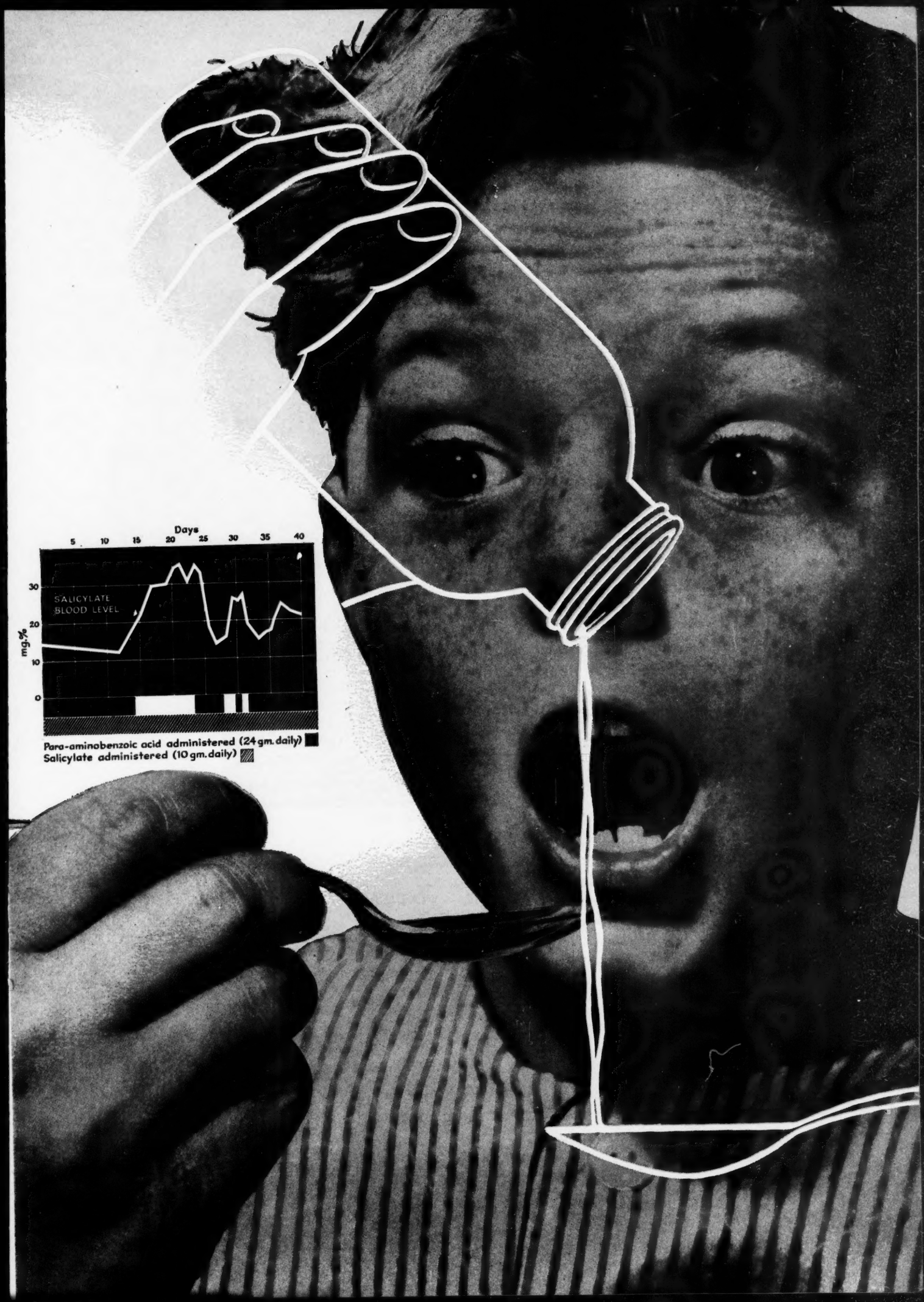
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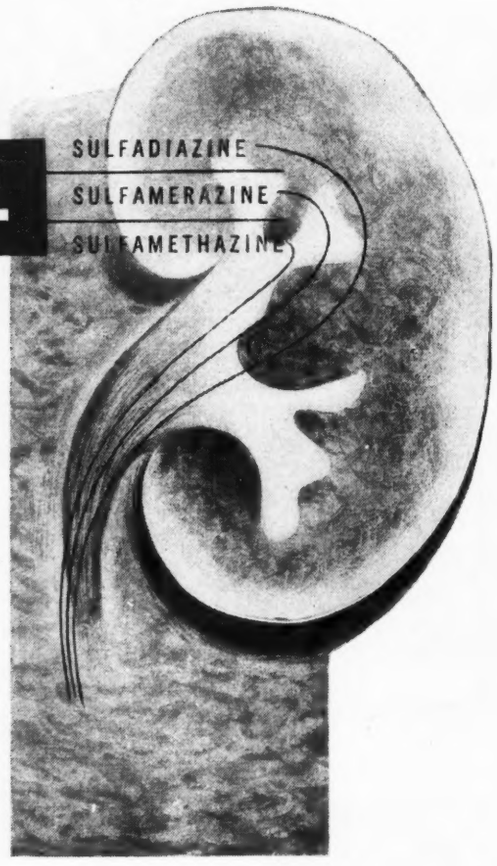

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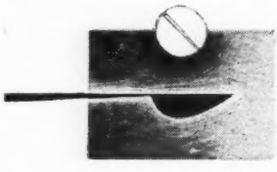

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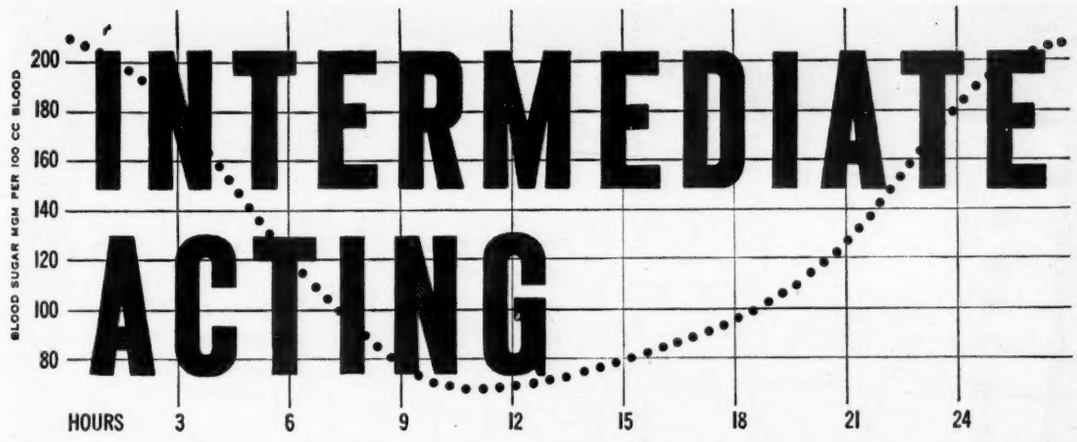

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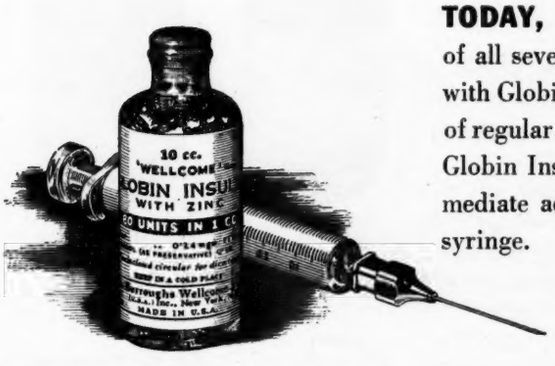

1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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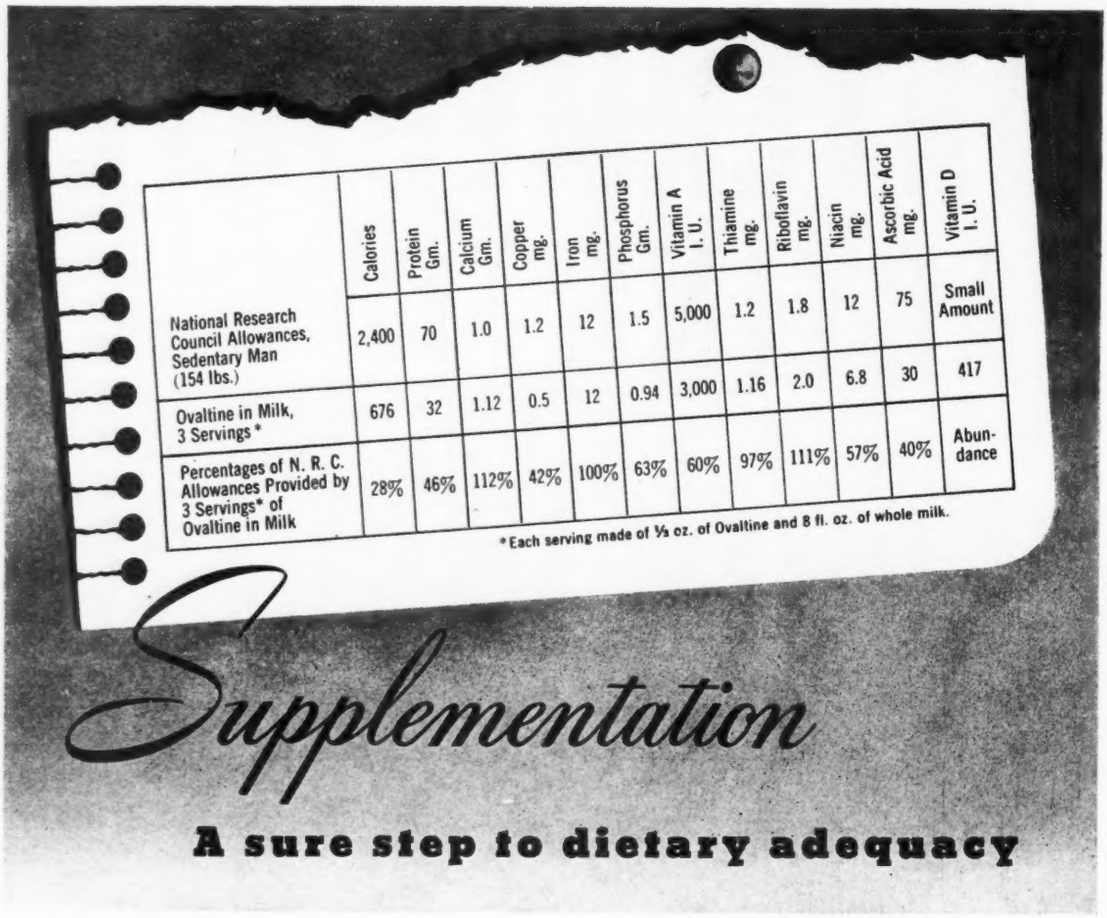

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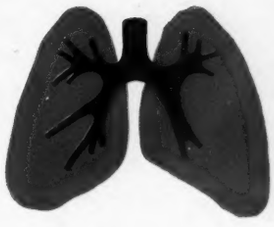

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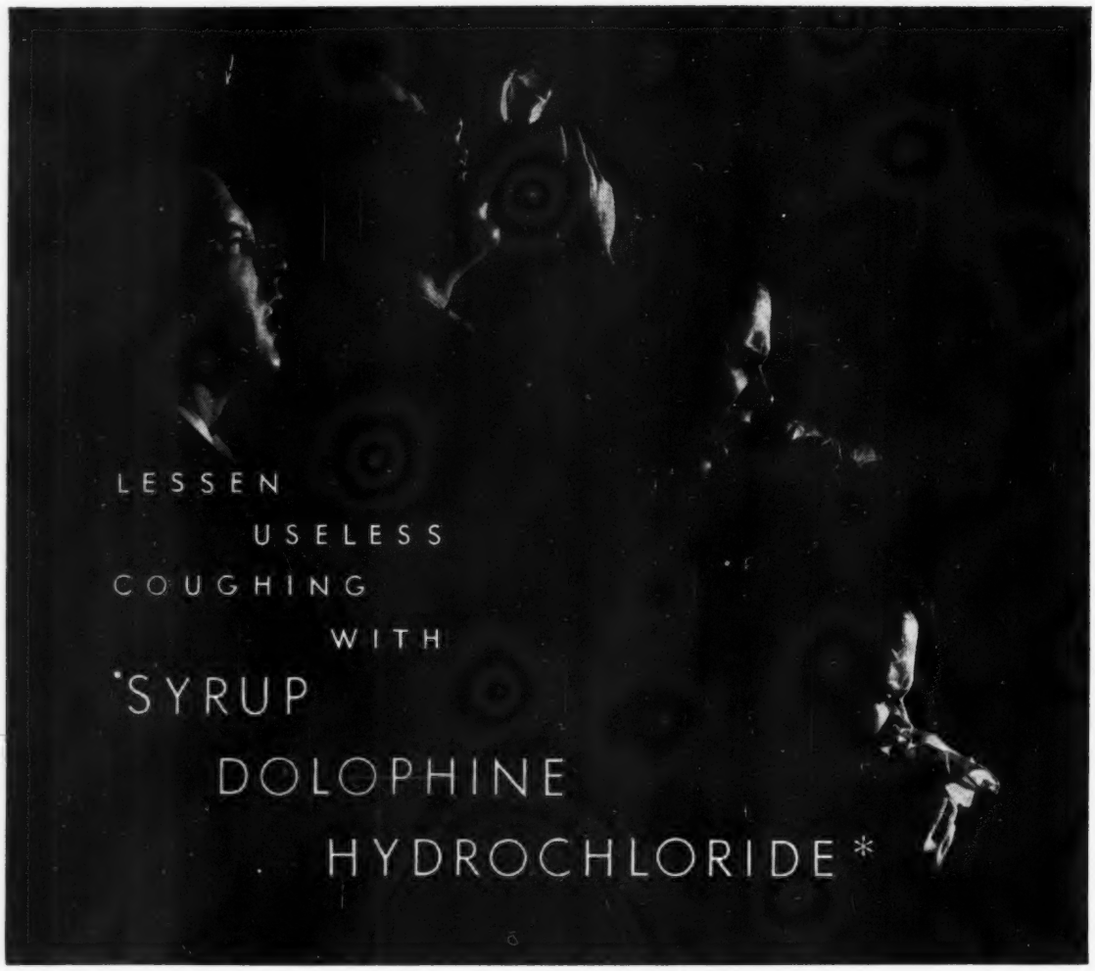

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The American Journal of Medicine

VOL. VII DECEMBER, 1949 No. 5

Editorial

Infectious Mononucleosis

FOR the third time in this century infectious mononucleosis is enjoying a new peak of attention. It is convenient to divide the history of infectious mononucleosis into four periods. The first period was that of clinical description which opened in 1885 and ended with the discovery of the blood changes in 1920. The second period, dominated by the hematologists, lasted from 1920 to 1932 and it was during this time that infectious mononucleosis emerged as a clinical entity through the unification of at least three poorly defined and independent clinical pictures. Pediatricians recognized glandular fever, otolaryngorhinologists described monocytic angina and other forms of throat infection associated with changes in the lymphocytes, and internists knew of severe febrile illnesses with changes in the lymphatic system and in the blood which at times simulated fatal clinical pictures. These three disease groups were found to have an abnormal blood picture in common and studies of this culminated in the classic description of the hematology of infectious mononucleosis by Downey[1] in 1923. By the end of the hematologic period infectious mononucleosis had been firmly established as a clinical entity. The third, or serologic period, started in 1932 when Paul and Bunnell[2] were surprised to find sheep cell agglutinins in the serum of a patient with infectious mononucleosis. This additional laboratory method, available both for diagnosis and investigation, led to the extensive serologic studies that characterized the third period. In spite of the detailed descriptions of the blood cell morphology and growing utilization of the serologic reactions the problems of epidemiology, etiology, pathology and therapy remained unsolved. One difficulty was a lack of adequate knowledge regarding the pathology of infectious mononucleosis. The fourth period, that of pathologic description, opened in 1944. Since then pathologists have made three major reports based upon excellent autopsy studies. The publications of Ziegler,[3] Allen and Kellner,[4] and Custer and Smith[5] are based upon a total of ten autopsies. We now know that infectious mononucleosis is a generalized disease and that there are infiltrations of abnormal lymphocytes in almost every organ of the body.

The pathology of infectious mononucleosis is now clear. The basic lesion is a perivascular infiltration of both normal and abnormal lymphocytes which Custer and Smith[5] found in all tissues that they studied except the bone marrow. They believe these cells to be metaplastic and to be formed *in situ* from other cells of the reticulo-endo-

[1] DOWNEY, H. Acute lymphadenosis compared with acute lymphatic leukemia. II. Hematologic studies. *Arch. Int. Med.*, 32: 82, 1923.

[2] PAUL, J. R. and BUNNELL, W. W. The presence of heterophile antibodies in infectious mononucleosis. *Am. J. M. Sc.*, 183: 90, 1932.

[3] ZIEGLER, E. E. Infectious mononucleosis; report of a fatal case with autopsy. *Arch. Path.*, 37: 196, 1944.

[4] ALLEN, F. H., JR. and KELLNER, A. Infectious mononucleosis; an autopsy report. *Am. J. Path.*, 23: 463, 1947.

[5] CUSTER, R. P. and SMITH, E. B. The pathology of infectious mononucleosis. *Blood*, 3: 830, 1948.

thelial system. The cells are not considered invasive. The lesion may persist long after the patient is judged to be well.[4] This fundamental and characteristic lesion is not at all uniform in its distribution throughout the body, and in any individual patient may be most marked in the central nervous system, liver or lungs. The myocardial lesions which have been seen are rarely severe enough to cause more than transient electrocardiographic abnormalities; the renal infiltrations produce an interstitial nephritis but are not known to cause permanent disability. Alarming symptoms occur when the infectious mononucleosis infiltration is predominant in the central nervous system, and under these circumstances the clinical pictures of benign lymphocytic meningitis, encephalitis or the Guillain-Barré syndrome may be produced. Two fatal instances of the Guillain-Barré syndrome caused by infectious mononucleosis have been studied both by Custer and Smith[5] and by Ricker, Blumberg, Peters and Widermann.[6,7] When the infectious mononucleosis lesion is marked in the lungs, the clinical and x-ray pictures are those of primary atypical pneumonia. Both the clinical pictures and the pathologic lesions of infectious hepatitis and infectious mononucleosis with severe hepatitis can hardly be distinguished. Numerous studies of liver function have established that almost every patient who is ill enough to come to the attention of a physician has some degree of impairment of liver function.[8,9] Watson and his co-workers[9] have just reported their studies upon twenty-five patients with infectious mononucleosis and find a significant increase in the total urinary coproporphyrin excretion. The increase is usually found in association with other evidence of functional impairment of the liver. The splenic lesion is characteristic, with lymphocytic infiltration and thinning of the capsule and dissolution of the trabeculae. Smith and Custer[10] describe this as a weakening of the basic structure of the spleen. The expanding splenic volume together with the structural weakness is dangerous and leads to occasional spontaneous rupture in the third week of the disease.

Infectious mononucleosis is one of the acute reticulo-endothelioses; almost certainly infectious in nature and, from the immunologic pattern, it is an infection that could hardly be bacterial in nature. So far, transmission experiments both with experimental animals and human volunteers have given conflicting results. The etiologic agent has not been identified.

The serologic mechanisms associated with infectious mononucleosis and with the sheep cell agglutinins usually demonstrable at some stage of the disease remain obscure. The antibody present in the serum of patients with infectious mononucleosis is not a true Forssman heterophile antibody.[11] Recent work by Schwarzweiss and Tomcsik,[12] based upon the demonstration by Stuart and his co-workers[13,14] of a thermostable heterogenetic antigen in beef erythrocytes, has resulted in the isolation of a heterogenetic "mononucleosis antigen" from the

[6] Ricker, W., Blumberg, A., Peters, C. H. and Widerman, A. The association of the Guillain-Barré syndrome with infectious mononucleosis. *Blood*, 2: 217, 1947.

[7] Peters, C. H., Widerman, A., Blumberg, A. and Ricker, W. A. Neurologic manifestations of infectious mononucleosis, with special reference to the Guillain-Barré syndrome. *Arch. Int. Med.*, 80: 366, 1947.

[8] Brown, J. W., Sims, J. LeR., White, E. and Clifford, J. E. Liver function during infectious mononucleosis. *Am. J. Med.*, 6: 321, 1949.

[9] Watson, C. J., Hawkins, V., Capps, R. B. and Rappaport, E. M. Studies of coproporphyrin. IV. The per diem excretion and isomer distribution in the urine in infectious hepatitis, infectious mononucleosis and mechanical jaundice. *J. Clin. Investigation*, 28: 621, 1949.

[10] Smith, E. B. and Custer, R. P. Rupture of the spleen in infectious mononucleosis. *Blood*, 1: 317, 1946.

[11] Bailey, G. H. and Raffel, S. Hemolytic antibodies for sheep and ox erythrocytes in infectious mononucleosis. *J. Clin. Investigation*, 24: 288, 1935.

[12] Schwarzweiss, H. and Tomcsik, J. Isolation of the heterogenetic "mononucleosis antigen" from the stroma of beef erythrocytes. *Proc. Soc. Exper. Biol. & Med.*, 69: 558, 1948.

[13] Stuart, C. A., Griffin, A. M., Fulton, M. and Anderson, E. G. E. The nature of the antibodies for sheep cells in infectious mononucleosis. *Proc. Soc. Exper. Biol. & Med.*, 34: 209, 1936.

[14] Stuart, C. A., Griffin, A. M., Wheeler, K. M. and Battey, S. A thermostable antigen in beef-cells. *Proc. Soc. Exper. Biol. & Med.*, 34: 212, 1936.

stroma of beef erythrocytes.[15] This antigen which is alcohol-soluble and heat-stable resists digestion by pepsin and inhibits the sheep cell agglutination by infectious mononucleosis serum in dilutions as great as 1:2,400,000. It can be separated from the serum sickness antigen also present in beef red blood cells.[16] This significant advance may, in time, improve our understanding of the Paul-Bunnell test.

Hitherto the disease has been underestimated, both in regard to its total effect upon young population groups and in its potential harm to the individual patient. Physicians who deal with military and student populations are well aware of the significant amount of lost time. Even when the disease is mild there are frequently prolonged periods of disability. The incidence seems to be increasing, perhaps as a result of increasing population density and of the population shifts of World War II. A similar increase in frequency occurred in England and in the United States following World War I.

Serologic and hematologic surveys made during epidemics have indicated that there may well be an enormous number of subclinical infections underlying the visible epidemiologic pattern of infectious mononucleosis. A carrier state is not impossible. As with diseases known to be caused by viruses, it is possible that infectious mononucleosis changes its character from time to time. Thus in the British epidemic of 1930 almost every patient had a skin rash but jaundice was not recorded. By 1935 to 1936 the picture had changed in England; the rash was seen less frequently and jaundice was relatively common. The hepatic, pulmonary and central nervous system manifestations of infectious mononucleosis, which are so evident at this time, may represent other changes in the potentialities of the unknown infectious agent. The evident danger to the community and to the individual makes necessary a more energetic attack upon the problems of etiology and forces us to consider the public health aspects more closely.

The treatment of infectious mononucleosis remains symptomatic and unsatisfactory. Bower[17,18] has had excellent therapeutic response in patients who were given gamma globlin. Evans[19] has recently reported a two-fold increase in the beta and gamma globulin of the blood in patients convalescent from infectious mononucleosis. Both of these observations will undoubtedly receive considerable further study. Patients should have some type of dietary management for their ever present hepatitis. When the disease has been marked by jaundice, it is probable that physical activity should be controlled during convalescence as it is with infectious hepatitis.

Infectious mononucleosis is no longer properly regarded as a diagnostic curiosity or as a benign and unimportant disorder. The disease always impairs vital organs, frequently incapacitates and occasionally kills.

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[15] SCHWARZWEISS, H. and TOMCSIK, J. [Über das physikalisch-chemische Verhalten der Antigen in Hammelblutstromata. *Schweiz. Arch. f. Path. u. Bakt.*, 11: 446, 1948.

[16] TOMCSIK, J. and SCHWARZWEISS, H. Nature of the heterogenetic hapten reacting with hemagglutinins in horse serum sickness. *Proc. Soc. Exper. Biol. & Med.*, 69: 562, 1948.

[17] BOWER, A. G. Infectious mononucleosis. *Arizona Med.*, 6: 17, 1949.

[18] BOWER, A. G., AFFELDT, J. E. and WEST, H. The treatment of the anginose type of infectious mononucleosis with gamma globulin. *J. Pediat.*, 35: 58, 1949.

[19] EVANS, A. S. Liver involvement in infectious mononucleosis. *J. Clin. Investigation*, 27: 106, 1948.

Clinical Studies

Radioiodotherapeusis*

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THE reports of other investigators[1,2] indicate that radioactive iodine can be used effectively in the treatment of thyrotoxicosis. In most of the early studies radioiodine with a half-life of twelve hours (I^{130}) was used but with the availability at low cost of isotope with a half-life of eight days (I^{131}) from Oak Ridge, Tennessee, the use of the latter has become more practical. We have treated 111 patients with radioiodine, chiefly I^{131}, and are reporting our results in this paper. Many factors concerned in the effectiveness of radioiodotherapeusis and the selection of optimal doses are discussed in the succeeding paper.[3]

TABLE I
TYPE OF 111 PATIENTS TREATED

Disease	No. of Patients
Thyrotoxicosis	106
Non-toxic nodular goiter	3
Malignant adenoma	2

TYPES OF PATIENTS TREATED

With the exception of one subject with a thymergastic reaction all of the thyrotoxic individuals who sought treatment during the period from December, 1946, to December, 1947, were treated with radioiodine. As shown in Table I there were 106 of these. Three received I^{130} and 103 received I^{131}. In six of the 103 patients treatment was begun only in the last three months so they are omitted from discussion. Five patients had no evidence of thyrotoxicosis at the time of radioiodotherapeusis; three had nontoxic nodular goiter and two had malignant adenoma.

Of the ninety-seven patients who received I^{131}, ninety-three (Table II) had previously been treated with one of the thiouracils; fifty-six of these had received such therapy for four months or longer. However, radioiodine was never given immediately after a long course of one of the thiouracils. Some of the patients had had serious toxic reactions to thiouracils and a few had had untoward reactions to iodide. Twenty-one had undergone one or more subtotal thyroidectomies;‡ further operative care would have been difficult in a few individuals.

TABLE II
PREVIOUS TREATMENT OF NINETY-SEVEN PATIENTS

	No.
Subtotal thyroidectomy	21
Thiouracil* treatment	93
0–4 months	35
4–8 months	18
8–16 months	30
16–24 months	10

* The term "thiouracil" is used to include not only the parent compound but also its derivatives. With few exceptions, however, it refers to 2-thiouracil and 6 n-propylthiouracil.

Of the seventy-six individuals not previ-

‡ In the presentation of data we have considered in a separate class patients who had been previously thyroidectomized because of greater difficulties in evaluating the characteristics of the thyroid glands and because of a possible difference in their response.

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† Research Fellow aided by the Commonwealth Fund.

ously operated upon twenty-two had a nodular goiter* and fifty-four had diffuse hyperplasia of the thyroid. There were essentially the same number of cases with mild, moderate and severe disease. (Table III.) The ages of the patients (Table IV) ranged from fifteen to seventy years. There were twice as many females as males.

TABLE III
SEVERITY OF THYROTOXICOSIS

	No.
Mild	32
Moderate	33
Severe	32

At the time radioiodine was given several of the patients had congestive heart failure, one was suffering from acute glomerular nephritis and another had chronic pyelonephritis. Three individuals had had acute hepatitis within a few months prior to therapy. One patient received a single dose of I^{131} during the first two months of her pregnancy.

PLAN OF THERAPY

Before each patient was given radioiodine the degree of thyrotoxicity was evaluated clinically and by means of determinations of the basal metabolic rate. Special attention was given to the type and duration of previous therapy and to the size,† configuration and consistency of the thyroid. The characteristics of the gland together with the clinical status of the patient proved ultimately to be the most useful criteria in selecting the initial dose of radioiodine and in establishing the need for subsequent administration of isotope.

All I^{131} was obtained from Oak Ridge and the radioactivity of the isotope at the time of its administration was based upon the standards of the laboratories‡ which provided the isotope. Prior to its ingestion by the patient the stock solution was diluted with distilled water so that 10 ml. contained 1 mc.* In the majority of patients 0.3 to 0.5 mg. of potassium iodide was employed as a carrier. On eleven occasions 50 mg. of this compound were given; fifteen patients received 2 Gm. of sodium bromide with the I^{131}.

TABLE IV
AGE AND SEX DISTRIBUTION OF NINETY-SEVEN PATIENTS

Age Decade	No. of Patients
11–20	5
21–30	21
31–40	19
41–50	23
51–60	20
61–70	9
Male	33
Female	64

Of course, the selection of dosage was the greatest problem; many aspects of this are presented in the succeeding paper.[3] Initially we attempted to ascertain how much of the radioiodine was stored in the thyroid gland following tracer (100 μc) or therapeutic doses. Among the methods used were epithyroid counts; early, medium and late changes in the total and protein-bound radioiodine concentration of the serum; urine excretion studies and combinations of these. However, we soon found, as presented in the next paper,[3] that none of these methods was a very accurate indicator of the dosage that would be required ultimately. Early we adopted the policy, which was explained to each patient, that it was much easier to give one or more additional doses than to treat a myxedematous state that might result from larger doses. Therefore, we attempted to give the very minimal

* We apply the term "nodular goiter" only when we are of the impression that circumscribed nodules are present.

† Upon each visit of the patient specific estimation was made of the size of the gland. It is believed that satisfactory evaluations can be made in most of the patients when the gland is less than approximately 70 Gm. (see Appendix).

‡ The Clinton Laboratories of the Monsanto Chemical Co., Oak Ridge, Tenn.

* Upon arrival of a consignment of I^{131}, usually 75 to 100 mc., it was moved promptly to a special laboratory where the dilution was accomplished with minimal exposure. The stock solution was kept in an enclosure of two-inch lead bricks. Essentially all of the isotope was dispensed on the day of its arrival and the return of the patients to widely separated communities lessened the concentration of radioactive material in a confined region. Dental roentgen-film badges were worn by all personnel who worked with the stock solution. Random monitory counts throughout the laboratory showed minimal contamination.

TABLE V
ADJUNCTIVE THERAPY

Treatment	No. of Patients		No. of Treatments
	No Treatment	Treatment	
Thiouracil Pre-I*	24	73	112
KI Carrier	3	94	199
KI Post-I*	46	51	77

* This therapy was given for a few weeks preceding the radioiodotherapeusis, usually being discontinued three or four days before the latter. It is not to be confused with the thiouracil therapy given for four months or longer to fifty-six patients. The latter was discontinued at least one month before the isotope treatment.

quantity which we decided might be necessary. In most patients the initial dose was from 3 to 7 mc.

In our initial experiences with radioiodotherapeusis it was found that three patients who were treated with nothing but radioiodine experienced an exacerbation in thyrotoxicity of the nature of a thyroid storm. This was prevented in subsequent patients by using propylthiouracil, usually from 200 to 300 mg. daily, for a few weeks before the radioiodine, discontinuing its use approximately four days before the latter. In many cases additional aid was afforded by the administration of potassium iodide, 3 drops twice daily for five days, beginning the day after the radioiodine. In Table v is presented the number of times

TABLE VI
EFFECT OF DURATION OF PREVIOUS TREATMENT WITH THIOURACILS UPON DOSAGE OF RADIOIODINE REQUIRED TO PRODUCE REMISSION WITHIN SIX MONTHS IN PATIENTS WITH DIFFUSELY HYPERPLASTIC GOITERS
(NONE HAD BEEN OPERATED UPON)

Thiouracils (months administered)		0	0–4	4–8	8–16	16–24
Total mc.	R	6–11.3	4.5–16	5–12	3.5–16.5	2–11
	M	8.4	9.1	8.4	7.1	6.4
	SD	2.6	4.2	2.1	3.5	3.9
Number of doses	R	1–3	1–4	1–3	1–4	1–2
	M	1.7	2.3	1.7	1.7	1.5
	SD	1.0	0.9	0.7	0.3	0.2
μc/Gm. thyroid	R	150–177	112–400	155–300	133–366	66–275
	M	164	251	233	221	174
	SD	13.5	93.5	57.2	81.4	91.2
μc./Gm. thyroid/month*	R	75–88	56–100	50–150	45–125	33–71
	M	82	82	86	76	56
	SD	6.6	13.2	34.5	22.2	17.7
μc./Gm. combined weights of thyroid*	R	150–177	182–266	120–280	100–200	120–170
	M	164	210	172	149	145
	SD	13.5	29.0	64.8	43.3	35.4
Months before remission	R	1–2	2–6	1–3	1–4	1–5
	M	1.7	3.3	2.3	2.3	2.2
	SD	0.6	1.0	0.9	1.5	1.9
No. of Patients	..	3	12	8	15	4

R = range
M = median
SD = standard deviation

* For a discussion of these calculations, see footnote in text. In calculating μc./Gm. thyroid/month only the quantity of isotope used per month in the first six months was included.

that propylthiouracil and potassium iodide were used in conjunction with the radioiodine therapy.

Six patients were hospitalized at the time radioiodine was given; the remainder were followed quite satisfactorily through their periodic visits to the laboratory. Ordinarily patients were seen during the first week after receiving the isotope and then at intervals of two weeks throughout the first two and a half months. Up to the sixth month the patients were seen once a month and at bimonthly intervals thereafter. It was necessary to follow some patients much more closely than this.

TABLE VII

COMPARISON OF DOSAGES OF RADIOIODINE USED TO PRODUCE REMISSION IN SIX MONTHS IN PATIENTS PREVIOUSLY TREATED WITH THIOURACILS FOR LESS THAN FOUR MONTHS* WITH THOSE REQUIRED FOR PATIENTS WHO HAD NODULAR GOITER OR WHO HAD PREVIOUSLY HAD THYROIDECTOMY

Group		Diffuse Goiter	Thyroidectomy Previously	Nodular Goiter
Total dose mc.	R	4.5–16	4–11	4–36
	M	9.1	7.7	14.7
	SD	4.21	2.38	11.3
Number doses	R	1–4	1–2	2–5
	M	2.3	1.5	2.4
	SD	0.9	0.17	1.5
μc./Gm. thyroid	R	112–400	133–296	160–319
	M	251	197	216
	SD	93.5	58.9	59.9
μc./Gm. thyroid/month†	R	56–100	34–125	40–100
	M	82	73	66
	SD	13.2	34.3	18.8
μc./Gm. combined weights of thyroid†	R	166–230	88–153	89–131
	M	210	110	115
	SD	29	29.4	15.4
Months before remission	R	2–6	1–4	1–5
	M	3.3	2.0	3.3
	SD	0.96	1.17	1.6
No. of patients		12	8	13

R = range
M = median
SD = standard deviation

* Only those patients treated with thiouracil for less than four months are included in this analysis; treatment for longer intervals is more likely to influence the results.

† For a discussion of these calculations, see footnote in text.

RESULTS OF THERAPY

Ninety-two of ninety-seven thyrotoxic patients treated with I^{131} experienced a sustained remission* of thyrotoxicosis; mild hyperthyroidism persisted in five; persistent myxedema developed in three.

TABLE VIII

DURATION OF SUSTAINED REMISSIONS

Months	Diffuse Hyperplasia	Thyroidectomy	Nodular Goiter
1–4	7	..	4
4–7	6	2	1
7–10	24	7	10
10–13	14	9	3
13–16	3	2	..

I. Sustained Remissions. 1. *Interval Preceding Onset; Duration:* In eighty-three subjects (86 per cent) remissions with sustained euthyroidism were observed within six months following initial therapy with radioiodine. Six patients who exhibited evidences of thyrotoxicosis six months after their initial treatment subsequently became euthyroid. The duration of previous thiouracil therapy had no significant effect upon the promptness of those responses which occurred within the six-month period in patients with diffuse hyperplastic goiters. (Table VI.) The median values of the duration of the intervals between the initial I^{131} treatment and the establishment of remissions in patients treated with thiouracil for less than four months were as follows: 3.3 months in patients with diffusely hyperplastic goiters; and 2.0 months in patients who had previously undergone thyroidectomy. (Table VII.) Although the response to radioiodine was somewhat more prompt in the last group, the differences are not statistically significant. The duration of remissions thus

* "Sustained remission" is applied to patients who have become euthyroid and have remained so for more than one month.

far is shown in Table VIII. The degree of permanency of the remissions must await more prolonged observations. One of the five patients who did not have a remission disappeared from observation after only one dose had been given. Some additional data in the case are given in Figure 6 of the succeeding paper.[3] The thyroid glands of each of the other four have decreased to a normal or subnormal size and it is believed that none will require more than a small amount of additional therapy, if any.

TABLE IX
TOTAL NUMBER OF DOSES OF RADIOIODINE

No. Doses	No. of Patients with Sustained Remission	No. of Patients without Sustained Remission
1	32	1
2	28	..
3	21	1
4	7	..
5	3	1
6	..	2
7	1	..

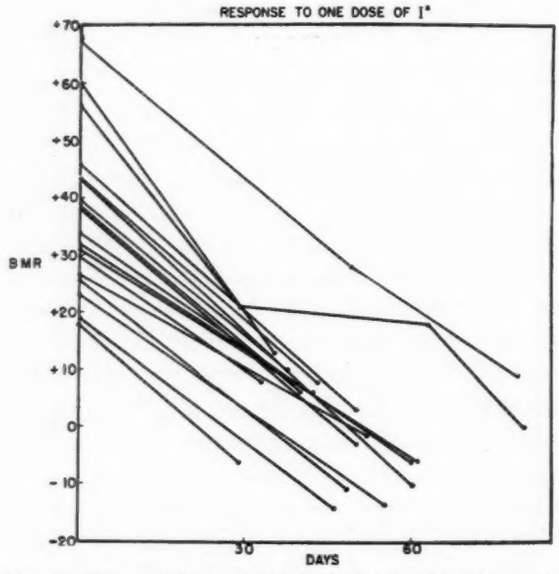


FIG. 1. None of the patients included in this plot had received radioiodine previously. Each individual experienced a remission following one dose of the isotope which has been maintained subsequently; none developed myxedema.

2. *Dosage of Radioiodine:* A total of 222 doses was given to ninety-seven patients, an average of 2.2 doses per subject. (Table IX.) In thirty-two individuals only one dose, 2 to 8 mc. was required to produce a sustained remission, the average being 5.3 mc. The decrease in the basal metabolic rate in a representative group of these patients is shown in Figure 1. Some individuals required several doses before a remission was produced. (Fig. 2.)

TABLE X
TOTAL DOSAGE OF RADIOIODINE ADMINISTERED BEFORE SUSTAINED REMISSION OCCURRED

Total Dosage mc.	No. of Patients with Sustained Remission		
	Within Six Months	After Six Months	None
2	1		
3	2		
4	11	1	
5	9		
6	10		
7	9	..	1
8	5		
9	6		
10	5	1	
11	6		
12	3	..	1
13	4		
14	2	2	
15	2	1	
16	2		
18	..	1	1
20	1	1	
21	..	1	1
25	2	1	
27	..	..	1
30	1		
36	2		

As shown in Table VI and discussed in the following paper,[3] the duration of previous therapy with thiouracil did not exert a statistically significant effect on the quantity of radioiodine required; however, experiences with individual patients make us entertain the possibility. This group of patients was given an average of approximately 8 mc. divided into two doses. Patients who had been previously thyroidectomized also required approximately 8 mc.

The largest doses were given to the twenty-two subjects with toxic nodular goiters; each individual received an average

of about 14 mc. Each of two such patients was given a total of 36 mc. divided in the manner indicated in Figure 3. Doses equal to twice the amount needed to produce myxedema in some patients with diffuse toxic goiter were tolerated with relative impunity in certain subjects with toxic nodular goiter. Some of the patients were much more refractory than others (Table x) irrespective of whether the gland was nodular; fourteen required more than three doses and one required seven. As discussed in the next paper, many factors are concerned in determining the dosage of radioiodine required. Two important factors are the characteristics of the thyroid gland and the interval between treatments.* These factors are partially considered in Tables vi and vii. Approximately 225 μc. of radioiodine per Gm. of thyroid weight was required to produce remission. When calculated in the manner described in the foot-

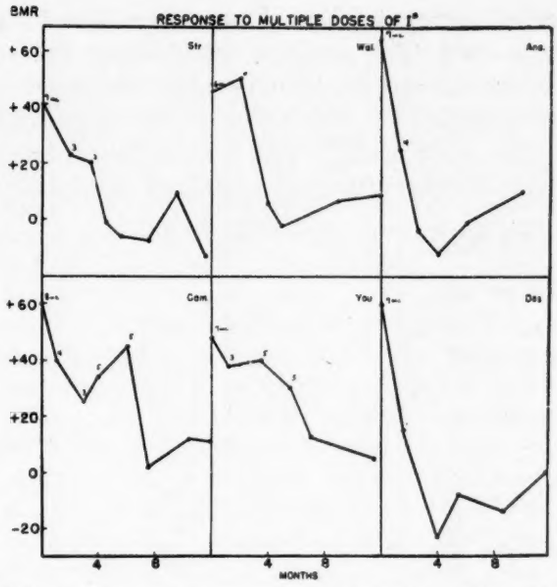


FIG. 2. The small numerals indicate the number of millicuries of radioiodine administered. Note that the decrease in basal metabolic rate was fairly precipitous once an adequate dose had been given.

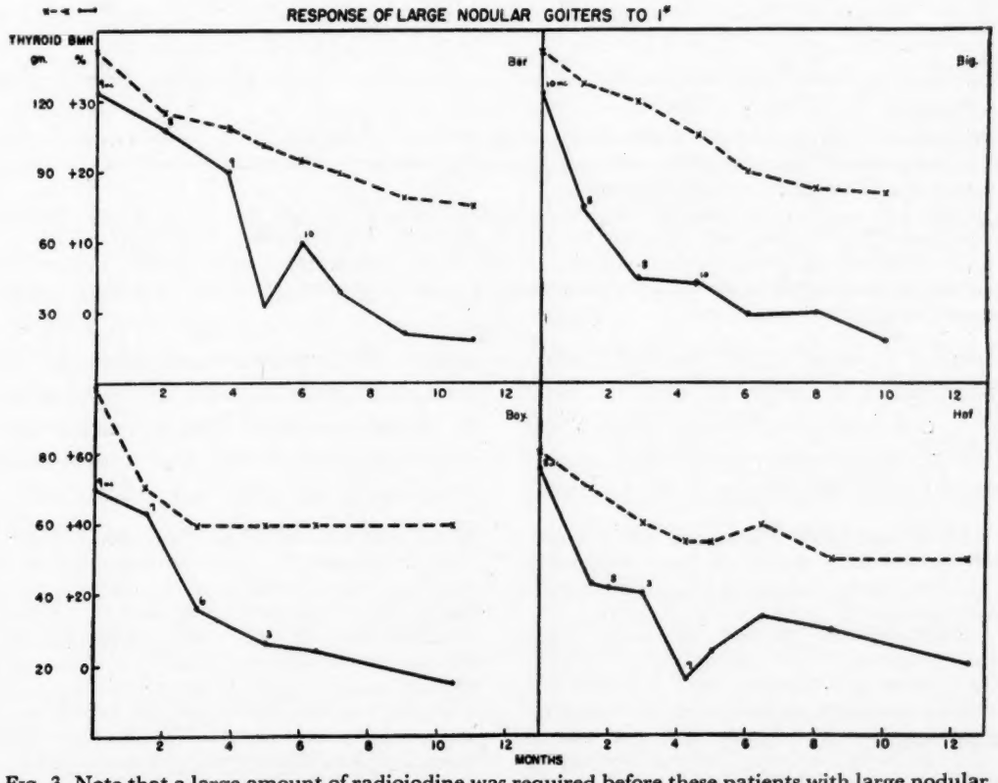
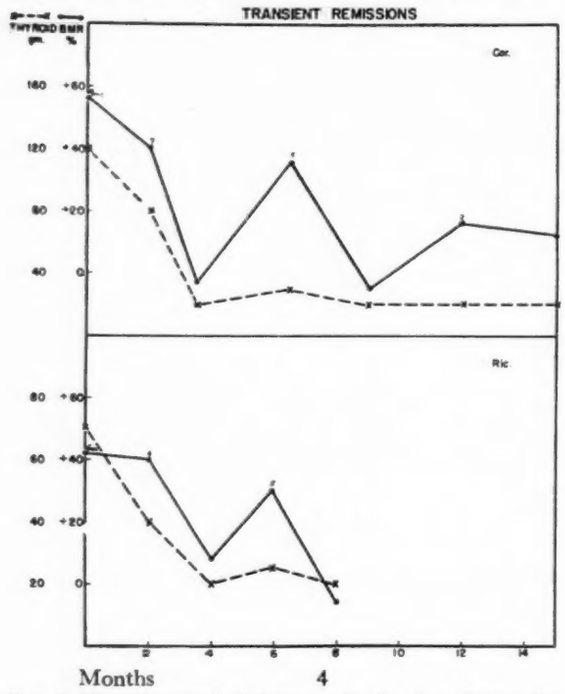


FIG. 3. Note that a large amount of radioiodine was required before these patients with large nodular goiter experienced a remission of their thyrotoxicity. In each case the size of the goiter decreased to some extent and thereafter showed little change in spite of the large doses of radioiodine. It may be observed that patient Big. received 18 mc. after reaching a state of euthyroidism, without significant effect upon the metabolic rate.

note* around 75 μc./Gm. thyroid/month was used. The patients with diffuse goiter required more μc./Gm. of combined weights of thyroid (Tables VI and VII) than did those with nodular goiter and the patients who had been thyroidectomized previously.



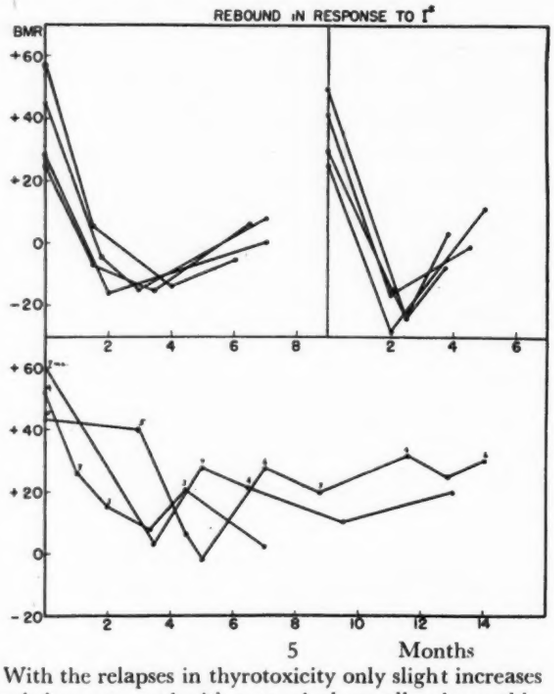


FIG. 4. Note the marked decrease in the size of the goiters. With the relapses in thyrotoxicity only slight increases in thyroid size occurred. Note that the second and third remissions occurred with successively smaller doses; this, however, has not been true in certain other cases.

FIG. 5. In the two top charts the subnormal response in metabolic rate in eight patients is shown. The maximal decrease occurred between two and four months after radioiodotherapy; within approximately six months the range had become normal. None of these patients has developed thyrotoxicosis subsequently. The lower graph demonstrates how the metabolic rate may be temporarily normal but increase thereafter to a degree sufficient to require more therapy.

II. Complete Transient Remissions and Transient Hypothyroidism. Some of the patients developed complete remissions that were only of short duration as exemplified by the response in the basal metabolic rate, shown in Figures 4 and 5. It can be observed in one instance (Fig. 5) that there was a transient remission after 10 mc. were administered but 17 mc. given in the next seven months failed to produce another remission. On the other hand, one patient (Fig. 4) experienced his first remission after 11 mc., the second after 5 mc. and the third after 2 mc. A third subject (Fig. 4) experienced no response after 5 mc. but a short remission was induced after an additional 4 mc.

* The following example is given as an indication for considering the amount of treatment given per month. A patient with a gland weighing 50 Gm. might experience a remission if 8 mc. were given as an initial dose, whereas thyrotoxicity would be likely to persist if 4 mc. were given initially and 4 mc. two months later. Thus the time factor must be considered. Since it takes about two months or longer for the maximal clinical effect to be exerted, we have empirically used this interval for convenience as the average interval needed for evaluating the action of each dose. Most of the injurious effect of the isotope would occur in the first four weeks. However, additional time is required for the inactivation of hormone that had been manufactured previously.

The patient, mentioned above, who was given 8 mc. in one dose received 80 μc./Gm./mo.; if given 4 mc. in each of two doses he would have received 40 μc./Gm./mo. Since this calculation fails to take into consideration the amount of decrease in the size of the gland which occurred between the first and second treatments, another calculation was made, μc. I*/Gm. "combined" thyroid weight. Applying this calculation to the above example, the two doses would be added together and the initial thyroid weight would be added to the weight estimated immediately preceding the second dose. If the latter was 30 Gm., by dividing the sum of the millicuries by the sum of thyroid weights, the average μc. I*/Gm. combined thyroid weight (or average thyroid weight) is obtained. In addition to the foregoing calculations the μc. I*/Gm. of thyroid was determined for each dose.

Following 5 mc. the patient developed a complete remission which has persisted for eight months.

As a consequence of treatment with I^{131} one patient developed transient hypothyroidism which, however, was of such long duration as to merit further discussion:

This patient (*Lac.*) first began treatment of moderately severe thyrotoxicosis in 1944 at the age of twenty-seven. She took thiouracil continuously for nine months but promptly relapsed after cessation of therapy. Thiouracil therapy was again instituted for a period of ten months and again there was a reappearance of thyrotoxicosis after the drug was withdrawn and the BMR rose to plus 20 per cent. The estimated weight of the thyroid at this time was approximately 25 Gm. The patient was given 4 mc. of I^{131} under these circumstances; two months thereafter the BMR was minus 13 and one month later was minus 29. The patient took desiccated thyroid intermittently throughout the next eight months. She has now received no thyroid medication for four months, is clinically in a euthyroid state and the metabolic rate is minus 9 per cent. She is in the third month of pregnancy.

There were fifteen other patients who developed significant temporary hypothyroidism which lasted for one to six months. Five of them were given desiccated thyroid for intervals of two to eight weeks but it has not been necessary for any of them to take this therapy for the last three months, with the exception of one patient with severe acute pituitarigenic ophthalmopathy. The latter patient did not have evidence of myxedema while not receiving thyroid for six weeks.

III. Complications of Therapy. 1. *Persistent Myxedema:* Only three patients developed lasting myxedema subsequent to the administration of I^{131}. As this constituted the only significant complication of such therapy, the pertinent points in each case are given in some detail:

Patient Sa.: When first seen in 1943 this man, aged fifty-two, had severe thyrotoxicosis with a goiter estimated as weighing 60 Gm. He was treated continuously with thiouracil for nineteen months and after the first month remained in remission throughout this period. However, by the sixteenth month of therapy the goiter had increased to 130 Gm.; during an interval of three months, 2,000 roentgen units were given over each lobe of the thyroid and the gland decreased to about 90 Gm. Thereafter he received several courses of therapy in the following order: methylthiouracil, potassium iodide, butylthiouracil and propylthiouracil. Therapy was interrupted after each course and thyrotoxicosis reappeared within a few weeks. Thirty months after the completion of roentgen therapy the thyroid had decreased to a weight of about 35 Gm., but three months after the cessation of all antithyroid therapy the metabolic rate was plus 43 per cent. At this time he was given 5 mc. of I^{131} with 0.3 mg. of potassium iodide and no other therapy. Two months later the BMR was minus 10 per cent; a month thereafter, minus 3 per cent and six months after receiving I^{131} it had fallen to minus 44 per cent. At this time no thyroid tissue was palpable and the patient presented a clinical picture typical of myxedema. During the past six months he has required continuous therapy with desiccated thyroid.

Patient Buc.: A female patient, aged twenty-seven, was found to have thyrotoxicosis in 1934 and therapy with thiouracil was instituted and continued for a period of eighteen months; during the last seventeen months of this period she was free of thyrotoxicosis. However, two months after the cessation of therapy thyrotoxicosis recurred. Thiouracil treatment was resumed for a period of three months and subtotal thyroidectomy was performed. Eleven months later there was a return of symptoms of hyperthyroidism and the basal metabolic rate was found to be plus 19 per cent. At this time she was given 5 mc. of radioactive iodine. Within six weeks the goiter and evidences of thyrotoxicosis disappeared and the basal metabolic rate was minus 14 per cent; within four months the patient became typically myxedematous and the metabolic rate had fallen to minus 35 per cent. Replacement therapy with desiccated thyroid was begun and has been continued to date, a period of about six months.

Patient Cl.: A housewife, aged thirty-four, had had a subtotal thyroidectomy in 1934 at the age of thirty-one. In 1944 thyrotoxicosis reappeared and she was treated with thiouracil for a period of nine months but a relapse followed cessation of therapy. Potassium iodide was then given for a period of six months but failed to control her disease and was supplanted by

propylthiouracil for a period of fourteen months. Withdrawal of the latter therapy was followed by a recrudescence of thyrotoxicosis and the basal metabolic rate rose to plus 23 per cent, although the estimated weight of the thyroid was only 15 Gm. At this time the patient received 4 mc. of I^{131}. Seven weeks thereafter the pulse rate was 120 per minute, there was a moderate amount of sweating and tremor and the metabolic rate was plus 19 per cent; an additional 3 mc. of radioiodine were given at this time. Two months after the second dose of I^{131} overt myxedema was apparent and the basal metabolic rate was minus 27 per cent. To date the patient has been maintained on desiccated thyroid for a period of eight months.

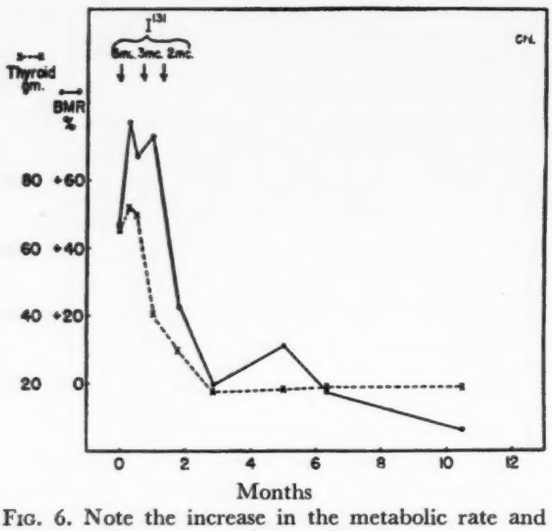


FIG. 6. Note the increase in the metabolic rate and gland size following radioiodine. The decrease in gland size preceded the decrease in metabolic rate. This patient received no specific therapy before or after the radioiodine.

The complications in the foregoing three patients were encountered relatively early in this study and occurred among patients who had previously been subjected to prolonged antithyroid therapy, thyroidectomy or roentgen therapy or a combination thereof. Under these circumstances it is frequently difficult to ascertain the requisite dose of isotope and subsequent experience suggests the use of relatively small doses in the treatment of patients who have had prolonged antithyroid therapy or in whom only a slight regrowth of tissue has occurred after thyroidectomy. Therefore, in the treatment of patients similar to Sa. and Buc., an initial dose of 3 to 4 mc. is now preferred over the 5 mc. which both individuals received. However, it must be emphasized that other patients with very similar clinical courses received as much or more therapy without the development of persistent myxedema. It appears quite likely that Cl. received the second dose of I^{131} prematurely; an interval of at least ten weeks after the initial dose would have afforded a greater margin of safety.

It is noteworthy that eight of the patients who developed transient hypothyroidism and two of those who developed myxedema had previously experienced subtotal thyroidectomy for the removal of a diffusely hyperplastic thyroid. On the other hand, no patient with a nodular goiter developed transient hypothyroidism or myxedema.

2. *Immediate Undesirable Effects:* During the first five days after the administration of I^{131} an occasional patient complained of mild headache, anorexia, nausea and malaise. These symptoms apparently did not depend upon the effects of radioiodine upon the thyroid. Among the patients whose thyrotoxicosis was associated with congestive heart failure, acute glomerular nephritis or chronic pyelonephritis there were no ill effects related to the complicating disease. The three patients who had had severe hepatitis apparently suffered no deleterious effects from I^{131} and the woman who received radioiodine during the first two months of pregnancy gave birth to a normal baby.

Three patients developed a very distinct, and several others a milder, exacerbation in the severity of thyrotoxicosis within the first week after the administration of I^{131}. The more severe reaction may be illustrated by the following case:

A Chinese girl, aged twenty-three, had moderately severe thyrotoxicosis and the diffusely enlarged thyroid weighed approximately 65 Gm. The basal metabolic rate was plus 48 per cent and, without antecedent therapy, she was given 6 mc. of I^{131}. On the third day she complained of pain and increased fullness in the region of the thyroid; by the sixth day, a marked increase in

FIG. 7. Note the marked decrease in the fullness of the neck. Only 4.5 mc. were required to produce a remission of thyrotoxicity and to reduce the thyroid to a size estimated as 10 gm.; it had been 50 gm. Overcompensated hyperphagia accounted for the slight obesity observed in the photograph on the left.

restlessness, tremor, sweating and tachycardia was noted. At this time it was quite obvious that there had been a distinct increase in the size of the thyroid and the basal metabolic rate was found to be plus 70 per cent. (Fig. 6.) At no time had there been clinical or bacteriologic evidence of acute infection. Following this acute exacerbation there was rapid improvement and decrease in the size of the thyroid; three weeks after the administration of the initial dose of I^{131} the weight of the thyroid was approximately 40 Gm. Subsequently three and two millicurie doses of I^{131} were given; the thyroid ultimately returned to normal size and the patient has remained free of thyrotoxicosis for a period of eleven months.

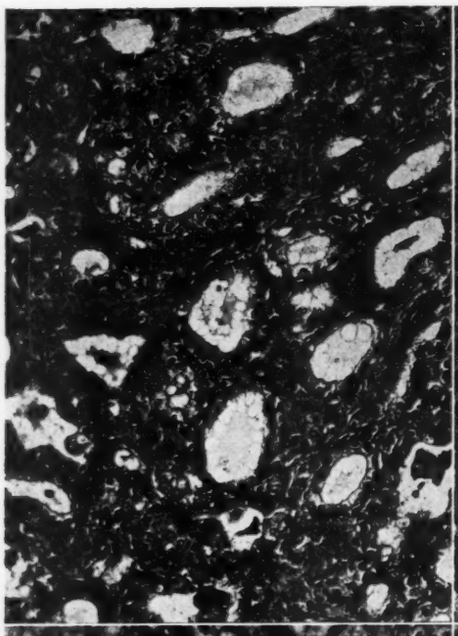
IV. Changes in the Thyroid Gland. 1. *Diffuse Thyroid Hyperplasia:* Except for the single patient who disappeared from observation, the thyroid decreased to an estimated weight of 25 Gm. or less in all individuals with diffuse goiter who received I^{131}. (Table XI.) The goiter usually regressed more rapidly than did clinical evidences of thyrotoxicosis which often persisted for a considerable time after the thyroid had assumed normal physical characteristics. Figure 7 illustrates the effects of I^{131} in decreasing the size of exophthalmic goiter in one individual; the most marked regression was noted in one patient whose estimated thyroid weight decreased from 120 to 20 Gm.

TABLE XI
SIZE OF THYROID GLAND BEFORE AND AFTER RADIOIODOTHERAPEUSIS

Grams	Diffuse Hyperplasia		Thyroidectomy		Nodular Goiter	
	Before	After	Before	After	Before	After
20	..	26	1	11	..	3
20–30	9	27	9	10	2	7
30–40	21	..	7	..	3	4
40–50	15	..	2	..	5	2
50–60	4	1	..	..	..	4
60–70	3	..	1	..	2	1
70–80	2	..	..	..	2	1
80–100	..	..	1	..	4	..
100 or more	..	..	..	..	4	..

These anatomic and metabolic effects of radioiodine are apparently produced by destruction of large masses of cells by radioiodine. During this study no attempt was made to investigate the morphologic changes in the thyroid immediately after the administration of I^{131}. However, it was possible to obtain sections of the thyroid in two patients who were euthyroid as a result of such therapy. Figure 8 shows the thyroid morphology two months after the administration of a single dose of 8 mc. of I^{131}. Figure 9 illustrates the changes in the gland

8A



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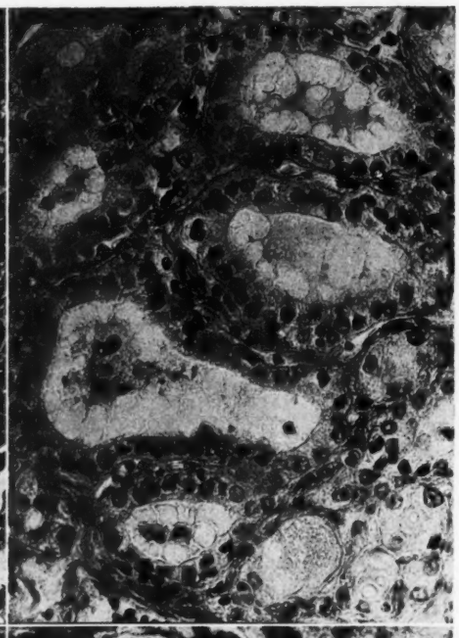

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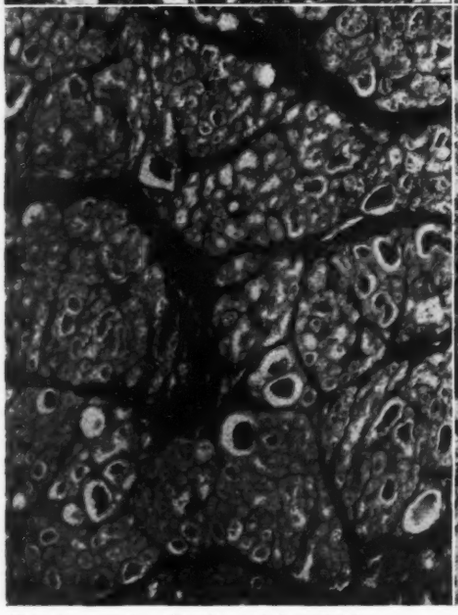

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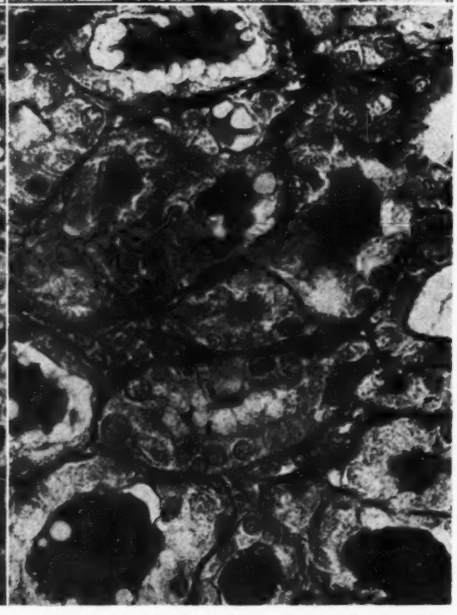

FIG. 8. A and B, Section of thyroid from a patient (Si.) who had had severe thyrotoxicosis. Before any radioiodine was given the gland was estimated as weighing 45 gm. and the basal metabolism rate was plus 70 per cent. Two months following the administration of 8 mc. of radioiodine clinical evidence of thyrotoxicity disappeared, the metabolic rate became normal and the gland decreased to 20 gm. At this time and without further preparation the anterior half of the lateral lobes of the thyroid gland and all of the isthmus were extirpated; the tissue removed weighed 12 gm. The patient has remained euthyroid for the subsequent six months. Note that only a relatively small amount of scar tissue is present and that all of the acinar cells appear active. The magnification in A is 400 ×; in B 800 ×.

FIG. 9. A and B, Naz. had severe thyrotoxicosis and 60 gm. of thyroid tissue. Several determinations showed the basal metabolic rate to be approximately plus 100 per cent. She was given 18 mc. of radioiodine in three doses within seven months. A state of euthyroidism was obtained within three months following the last treatment. The thyroid gland decreased to an estimated weight of 15 gm. At operation what appeared to be approximately one-half of the gland was removed; the tissue weighed 6 gm. Thus the gland had decreased to 25 per cent of its original size. The fibrous tissue, indicated by the black bands, encircles nests of hyperplastic acinar cells. Presumably large sheets of cells were destroyed in certain areas whereas the cells that remained viable continued to be active. The magnification in A was 100 × and in B 800 ×.

FIG. 10. Ber. was a female clerk, aged fifty-one, who had been known to have a goiter for twenty-two years. For several months she had had severe compression of the trachea associated with suffocating spells. Subtotal thyroidectomy was recommended but refused by the patient. After treatment with propylthiouracil for several weeks radioiodotherapeusis was given. (Fig. 3.) Following administration of 26 mc. of radioiodine a complete remission of thyrotoxicosis occurred and the pressure symptoms disappeared. The thyroid gland was estimated to weigh 140 gm. before therapy and 70 gm. thereafter; the measurements decreased from 7 by 6.5 cm. to 5 by 4.5 cm. The changes in the general appearance of the neck are shown in this illustration. An additional 10 mc. of radioiodine did not have very much effect on the basal metabolic rate nor the size of the goiter.

which were found after three doses of radioiodine; tissue was removed ten months after the initial therapy or three months subsequent to the third and last dose of I^{131}. A comparison of Figure 8 with Figure 9 reveals the greater degree of interstitial fibrosis in the latter. It is probable that the differences are related to the larger dose of I^{131} therapy in the latter. It is quite apparent that at this stage the evidence for loss of functioning thyroid cells is largely inferential; the cells which remain reveal no detectable abnormality under the microscope. It should be noted that partial thyroidectomy after I^{131} therapy offered no particular technical difficulty although a few adhesions were encountered between the thyroid and the adjacent tissues.

2. *Toxic Nodular Goiter:* Judging from the anatomic characteristics of such goiters it is not surprising that I^{131} frequently failed to bring about a reduction of the gland to normal size. Remaining relatively unaffected was that portion of the goiter made up of scar tissue and large colloid follicles or cysts. Although the hyperfunctioning adenomatous tissue might be markedly reduced, the remaining inert constituents persisted with little or no regression even though a euthyroid state had been achieved by radioactive iodine.

Figure 10 shows the changes which were produced in such a goiter by the repeated administration of I^{131} for a total dose of 36 mc. The thyroid, although still large, was reduced from *circa* 140 to 70 Gm. and symptoms of tracheal compression disappeared. Radioiodine was utilized only as a last resort in the treatment of this individual who steadfastly refused operation. It should be emphasized that the cosmetic results of I^{131} therapy are much less satisfactory for

toxic nodular than for diffusely hyperplastic goiters.

V. Treatment of Thyrotoxicosis with I^{130}. Only three patients were treated with radioiodine bearing a half-life of twelve hours (I^{130}). In each of these individuals the results were excellent as indicated by the following abstracts:

Wi., aged fifty-one, a female patient with thyrotoxicosis of moderate severity, after having failed to maintain a remission upon cessation of thiouracil therapy at the end of one year was given 30 mc. of radioiodine. Within three months her thyroid gland decreased from 50 to 20 Gm. and the thyrotoxicity disappeared. She has maintained a remission for two years.

Fe., a tailor, aged seventy-two, with severe thyrotoxicosis, after having responded with toxic reactions to orthophenylene thiourea and thiobarbital (?) and after insufficient improvement with propylthiouracil, was given 25 mc. of radioiodine. Within three months the thyroid gland decreased from 40 to 20 Gm. and the thyrotoxicosis subsided. He has maintained this remission for eighteen months.

Ru., a housewife, aged forty-nine, had moderately severe thyrotoxicosis. Within six months following 25 mc. of radioiodine the thyroid decreased from 30 to 20 Gm. and a remission of the disease was initiated; it has been maintained for eighteen months.

VI. Non-toxic Nodular Goiter. In an attempt to decrease the size of such goiters three individuals were given I^{131}. Therapy was, as anticipated, only moderately successful in spite of attempts to enhance the uptake of isotope by the preliminary use of thyrotropin and propylthiouracil. In one patient thyroidectomy fifteen weeks after the second dose of I^{131} provided tissue of some interest. Many nodules showed interstitial scarring similar to that seen in Figure 9 whereas others showed no change which might be ascribed to prior radioiodine therapy. Aside from the possible risk of covert malignancy it is apparent that such therapy accomplishes little in the management of non-toxic nodular goiters.

VII. Malignant Adenoma. Two patients with malignant adenoma were treated. Both had recurrence of tumor in the neck but generalized metastases could not be demonstrated in either. The course of both patients was quite similar and may be illustrated by the following summary:

Patient Bru., aged eighteen, had had a large nodular goiter removed six years previously. A diagnosis of malignant adenoma was made. Within two years nodules in the neck reappeared and these were removed; the changes microscopically were similar to those found after the first operation. At the time that radioiodine was administered there were three nodules in the neck which were from 1 to 2 cm. in diameter. With a tracer dose of radioiodine it was found that the uptake by the tissue was as good as in some patients with Graves' disease. (Fig. 2.) Following 5 mc. of radioiodine a moderate decrease in the size of the nodules occurred. Two months after the first treatment 8 mc. were administered. Within five months from the initial treatment the nodules had disappeared. The patient was in a state of euthyroidism at all times. The course of the second patient was similar; subsequent to the administration of 9 mc. of radioiodine the estimated 45 Gm. of tissue became impalpable.

COMMENT

The results that have been presented indicate that radioiodine can be used to produce a remission of thyrotoxicosis in essentially all cases. In 100 patients with this disease complete remissions have been produced and maintained for one month or longer in ninety-five. In each of the 100 patients treated the thyroid gland decreased in size. In most of the patients with diffuse hyperplasia the gland became essentially normal or subnormal in size.

Although the exact mechanism of "cure" in thyrotoxicosis (like its etiology) remains obscure, the question arises as to whether "cure" following radioiodine is on the same basis as that following thyroidectomy. Although there is a similar result in the two therapies in that the total number of cells is reduced, there is a possibility that additional antagonizing effects from radioiodine are attributable to sublethal actions on the cells and to secondary results from the fibrosis produced. However, experiences

with prolonged treatment with thiouracil suggest that a reduction in the total number of cells is not a necessity for a remission to persist after cessation of treatment. To serve as a working basis we use the hypothesis that the more "bombardment" individual thyroid cells receive from thyrotropin the more likely they are to become refractory to further stimulation; thus a remission of thyrotoxicosis would result when the thyroid cells develop an adequate amount of refractoriness. The fewer cells present, the more "bombardment" each receives. Eventually the cells, however, may lose some of their refractoriness. Other things being equal, the more cells which remain viable the greater is the likelihood of reappearance of thyrotoxicosis. This hypothesis could explain the remissions that occur following thyroidectomy, radioiodine or thiouracil, and would account for the greater incidence of relapses with the latter therapy.

The main problem in the use of radioiodine is the difficulty involved in the selection of the appropriate dose. Excessive amounts may produce myxedema but persistent myxedema was encountered in only three of our patients. Transient hypothyroidism has been not uncommon in our experience. So long as the hypothyroidism is only transient it does not constitute a significant handicap; indeed, such states seem to lend assurance to the persistency of the remission. Our experience has yielded the clinical impression that hypothyroidism is transient more frequently following radioiodotherapeusis than following thyroidectomy. If this observation is borne out by further experience, it might be postulated that with irradiation of the thyroid some of the acinar cells temporarily may have a decreased capacity to manufacture hormone, but may later regain their normal physiologic activity.

The patients who developed the full-blown picture of myxedema developed it more slowly (three to six months) than generally occurs following thyroidectomy. Some of the factors which may account for this difference in response are (1) with thyroidectomy a significant amount of hormone is removed along with the goiter, (2) following radioiodine many of the cells may continue to function at least partially for several weeks, either because this interval is required to kill the cells with radioiodine or for the scar tissue to contract enough to interfere significantly with their blood supply, or because of both factors.

Radioiodine can cause enormous reduction in the size of goiters but it does so chiefly by decreasing the number of acinar cells and probably secondarily by reducing the vascularity. It does not reduce the quantity of fibrous tissue or calcium, and apparently does not cause much reduction in colloid cysts. Therefore, in large toxic nodular goiters it can produce a complete remission in the thyrotoxicity and it can reduce the size of the goiter, but a large amount of inert tissue may persist. For this reason it probably will not offer much advantage in the treatment of the great proportion of large, non-toxic multinodular goiters.

The proper selection of patients for therapy with radioiodine must await further observation of individuals who have been treated in this manner and of those who have been given one of the thiouracils alone; more satisfactory comparisons with other methods of therapy can then be made. Upon the basis of present data, many factors should be considered in the selection of therapy for any individual patient.[4] Radioiodine is a very simple form of therapy to the patient but it must be used only by a selected group of specialists. Therefore, it is not available to very many people. This type of treatment is generally less expensive than is thyroidectomy and is associated with less economic strain and physical discomfort. It is particularly worth while in patients who have become sensitive to certain antithyroid compounds and to those in whom complications from thyroidectomy loom as a good possibility, for example, individuals with hemorrhagic tendencies, those with severe cardiovascular disturbances, those who have developed hypo-

parathyroidism or nerve paralysis after previous thyroidectomies. Relatively good results were obtained in the treatment of two patients with malignant adenomas. However, the results in patients with highly malignant neoplasms leave much to be desired.[5]

TABLE XII
COMPARISON OF THE CLINICALLY ESTIMATED WEIGHT OF GOITERS WITH WEIGHT OF THYROIDS REMOVED BY SUBTOTAL THYROIDECTOMY

Case No.	Weight of Thyroid (Gm.)	
	Estimated	Found
1	35	45
3	40	42
10	25	31
12	30	26
17	140	180
28*	40	29
36	40	39
43	35	32
52*	30	22
56*	30	28
57	50	44
58	60	50
60	40	34†
63	30	21
64	50	40
67	70	61
68	70	71
70*	35	23
73*	60	42
74	40	39
75	50	33
76*	50	71
83	80	90
84	60	63
85	35	25
87	70	60
91	60	66
101	50	43
103	30	24†
111*	60	60
114	40	32
119*	100	169
121*	120	140
124	15	12†
127	40	32
128	40	41
129*	40	49
134	70	73
139	30	23
140	50	44
146	35	35

* Adenomatous goiters.

† These values have been derived by multiplying the weight of one lobe by two since only hemithyroidectomies were performed.

The results in the three patients treated with I^{130} were excellent. Indeed, this isotope might be superior to I^{131} were it readily available. Its much shorter half-life causes it to exert its effect upon the thyroid and the other tissues within a much shorter interval. Thus, the other tissues are exposed to its damaging effects for shorter intervals. Whereas with the larger doses required the tissues get more exposure within a short interval, the sum total irradiation is less than with the I^{131} because a significant amount of the latter is fixed to protein, due to continued and more prolonged function, and can be demonstrated for many weeks. The use of tracer doses of radioiodine as an indicator of the quantity of isotope to use therapeutically is more applicable with I^{130} than with I^{131} because of the fewer oscillations in the rate of thyroid function.

Whether radioiodine in the doses used in this study will exhibit a significant carcinogenic effect and also its possible deleterious effects in other parts of the body remain to be determined.

SUMMARY

A total of 111 patients have been treated with radioiodine; 106 had thyrotoxicosis; three had non-toxic nodular goiter and two had malignant adenoma. Six of the thyrotoxic subjects received their treatment too recently for adequate consideration. In ninety-two of ninety-seven patients treated with I^{131} a remission was produced and has persisted. Most of these patients became euthyroid within six months, an average of approximately three months. A total of 222 doses of radioiodine were given to ninety-seven patients; an average of 2.2 doses per patient. Thirty-five required only one dose; fourteen were given more than three doses. In the group experiencing remissions within six months, approximately 225 μc. per Gm. of thyroid tissue were administered. An average total of about 8 mc. was required for thyrotoxic patients with diffuse hyperplasia of the thyroid and

those previously thyroidectomized; twenty-two individuals with toxic nodular goiter required larger total doses although somewhat smaller in proportion to the size of the thyroid gland.

The goiter was reduced in size in all instances. Indeed, in all except one of the patients with diffuse hyperplasia the gland decreased to an estimated 25 Gm. or less; the one exception was an individual who declined to return for completion of therapy. In most of the patients with diffuse hyperplasia the thyroid became reduced to essentially normal or subnormal size before remission resulted.

Three patients developed persistent myxedema. In sixteen others transient hypothyroidism resulted.

Three individuals with thyrotoxicosis were treated with I^{130} with excellent results. In two patients with malignant adenoma the cervical masses became impalpable. Three subjects with non-toxic nodular goiter experienced only slight reduction in the size of the goiters.

No significant untoward effects from the radioiodine were manifested by non-thyroid tissues. One individual was pregnant at the time of her therapy, one had acute glomerular nephritis, one had chronic pyelonephritis, three had had acute hepatitis and several had congestive heart failure.

An outline of our present plan of therapy and a discussion of many factors concerned with iodotherapeusis are given in the following paper.

Appendix. Since careful evaluation of the size of the thyroid is of importance in determining the dosage of radioiodine required, it is important to know how accurately this may be determined. There was no opportunity to weigh the gland of the patients before treatment with radioiodine. However, information obtained with other studies is of aid.

Several years ago one of us (R. H. W.) estimated the size of the thyroid of patients treated with thiouracil, and following subtotal thyroidectomy the gland was trimmed and weighed carefully as part of a procedure for determining the localization of thiouracil. The estimated and the determined weights of these glands are recorded in Table XII.

In interpreting the data it is to be borne in mind that the "determined weight" is not an exact indicator of the size of the gland as it exists in the patient because of variations in the amount of fluid lost or gained during the operation. Moreover, there were variations in the quantity of thyroid tissue left in the neck.

It may be observed that the error was greater in estimating the weight of adenomatous goiters than diffusely hyperplastic ones. In only three of thirty-one of the latter type was there a discrepancy of more than 10 Gm.

REFERENCES

1. Hertz, S. and Roberts, A. The use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.*, 131: 81, 1946.
2. Chapman, E. M. and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. *J. A. M. A.*, 136: 86, 1946.
3. Williams, R. H., Jaffe, H., Towery, B. T., Rogers, W. F. and Tagnon, R. Factors influencing the effectiveness of radioiodotherapeusis. *Am. J. Med.*, 7: 718, 1949.
4. Williams, R. H. Selection of therapy for individual patients with thyrotoxicosis. *J. A. M. A.*, 139: 1064, 1949.
5. Rawson, R. W. and McArthur, J. W. Radioiodine: its use as a tool in the study of thyroid physiology. *J. Clin. Endocrinol.*, 7: 235, 1947.
6. Williams, R. H., Jaffe, H. and Kemp, C. Effect of severe stress upon thyroid function. (In press.)

Factors Influencing the Effectiveness of Radioiodotherapeusis*

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RESULTS presented in the preceding paper[1] as well as in the reports of other investigators[2,3] demonstrate that in treating thyrotoxicosis with radioiodine some of the problems encountered are similar to those found with surgical therapy. The effectiveness of radioiodine, like subtotal thyroidectomy, depends upon the elimination of the majority of the thyroid acinar cells. Since only slight differences in the quantity and quality of tissue remaining may determine whether the amount of thyroid hormone produced is excessive, adequate or inadequate, it is imperative that this problem be evaluated carefully. An advantage is afforded surgical therapy by the opportunity of directly examining the gland, thereby aiding in determining how much tissue should be removed; the operator can proceed immediately in extirpating whatever amount he chooses. More difficulty is encountered in selecting the optimal dose of radioiodine. The concentration of and duration of fixation of isotope in or adjacent to thyroid cells[4] (Fig. 1) is a complex kinetic process which can be predicted only within certain broad limits. Even tracer-dose technics do not reflect the alterations in iodine metabolism that occur during the weeks that I^{131} exerts its activity. The efficacy of radioiodine in reducing the amount of hyperplastic tissue is subject to influences which relate to net iodine-thyroid-pituitary interrelationships which in turn affect the ionizing radiation to which the thyroid is subjected over a considerable period of time. In this respect, the ingestion of goitrogens, variation in iodine intake, metabolic rate, stress,[5] et cetera, should be mentioned.

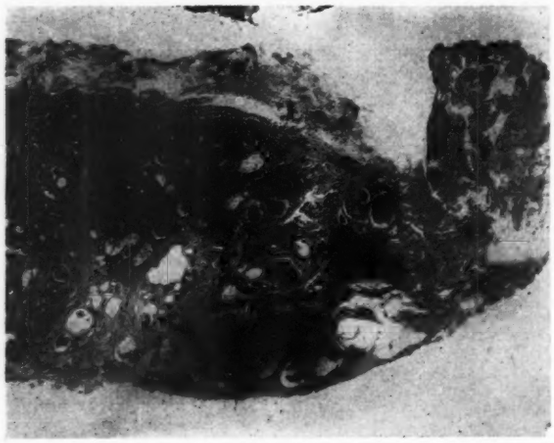

FIG. 1. Note the variations in the concentration of radioiodine in the thyroid.

In spite of certain difficulties inherent in the selection of dosage it is believed that radioiodine therapy is unquestionably the treatment of choice in certain patients and that its use is worthy of consideration in many others. Certain observations concerning the selection of doses of radioiodine in the treatment of 111 individuals with thyrotoxicosis are to be described.

METHODS

All of the radioiodine used in these studies was I^{131}. The quantities administered were based

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upon estimates made at Oak Ridge, Tennessee, with standard corrections for decay. All of the therapeutic doses were administered by mouth and consisted of 1 mc. per 10 cc. of water. In most of the treatments approximately 0.5 mg. of potassium iodide was used as a carrier. None of the subjects received potassium iodide within four weeks of the test doses except where otherwise mentioned. The tracer dose consisted of 100 microcuries in 1 cc. of physiologic saline solution without added carrier; it was injected subcutaneously.

For the determination of the radioiodine in serum 0.5 or 1 cc. was placed in a bottle cap with one drop of dupanol. After drying in an oven the cap was placed under a Geiger-Mueller tube and counts were made. Urine was assayed in a similar manner.

For the determination of PBI* 1 cc. of serum was pipetted into a 15 cc. centrifuge tube. Then 9 cc. of 10 per cent trichloracetic acid was added while the solution was stirred vigorously. After centrifugation the supernatant fluid was decanted. The precipitate was washed three times with 5 cc. portions of 10 per cent trichloracetic acid, transferred quantitatively to bottle caps, dried at 100°c. and then isotope counts were made.

Estimates of the size of the thyroid gland were made in all instances by the same physician and were recorded in Gm. It is believed that these estimations were relatively close, especially when the gland weighed less than approximately 70 Gm.[1]

The patients previously treated by means of thyroidectomy and those with nodular goiters are considered separately from those with diffuse goiter.

Fifty-six patients had received one of the thiouracils for prolonged intervals, as indicated in the figures. The dosage was sufficient to maintain the metabolic rate at a normal level.

RESULTS

Epithyroid Counts. Determinations of the concentration of isotope in the region of the thyroid gland were made in ten patients (Fig. 2) by placing a Geiger-Mueller counting tube successively over each lateral lobe of the gland. The counts were made twenty-four hours after therapeutic doses had been given. The counting tube was held 1 cm. from the skin and a leaded rubber pad was placed between the neck and the counter. In a few instances similar counts were made over the region of the kidneys.

The amount of radioiodine found in the thyroid region could not be correlated well with the ultimate total dose required to produce a sustained remission. The counts over each lateral lobe were quite similar. The counts over the renal regions were much less than over the thyroid. In one patient with severe acute glomerular nephritis (Per., Fig. 2) the concentration of isotope in the renal region was similar to that found in patients without kidney disease.

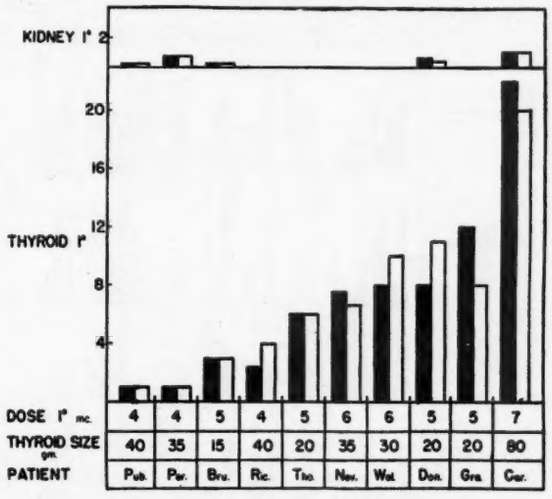

FIG. 2. In order to make allowance for the differences in the size of the thyroid gland in the correlation of the counts over the gland with the size of the dosage, the counts per second were divided by the dose in microcuries per 100 gm. of thyroid tissue. The same relative estimations were made with counts determined over the kidneys.

Relation of Radioiodotherapeusis to the Content of Radioiodine in Blood and Urine. 1. *Changes within One Hour after Tracer Dose:* Nineteen thyrotoxic patients received tracer doses of I^{131}. The subjects remained at rest for one hour and at this time determinations were made of the total amount of radioiodine which had been excreted and of its concentration in serum. A similar test was conducted in four athyreotic subjects and in seven normal individuals. The results are presented in Figure 3.

Considerable variation in the quantity of radioiodine in the serum and urine was

* Protein-bound radioiodine.

observed in the same as well as in different groups of subjects. Neither the content of isotope in the urine nor blood following the test dose was a satisfactory indicator of the quantity required to produce sustained remission. There was no significant difference between those who experienced a remission and those who did not.

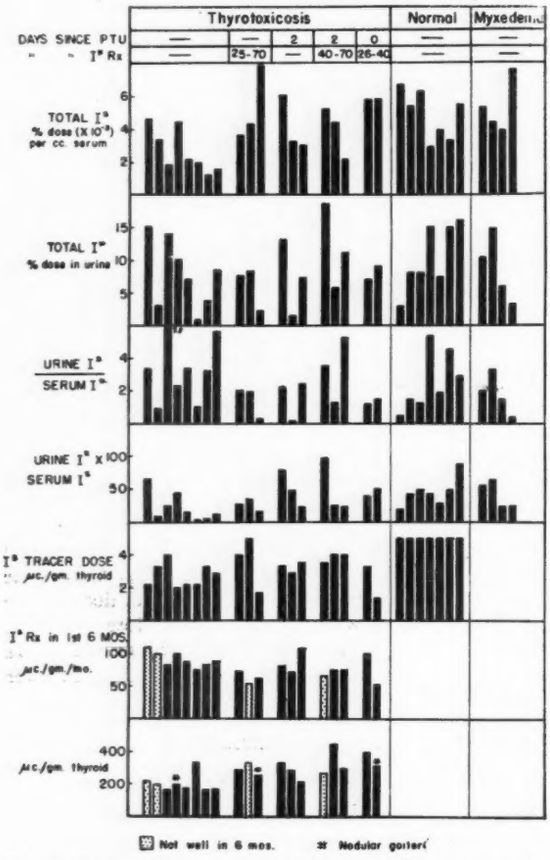

FIG. 3. Each column presents data in a different patient. All of the subjects experienced a remission within six months after the initial radioiodine treatment, except where indicated. The myxedema patients had been treated with desiccated thyroid for several months before the tests with radioiodine were conducted; their metabolic rates were within normal limits. The patients treated with propylthiouracil (PTU) had received from 200 to 250 mg. daily, ending at the times indicated. The thyrotoxic subjects previously treated with radioiodine had received therapeutic doses. Although some isotope was still present in these patients, the quantities were relatively insignificant. Tracer doses (100 mc.) were given each subject. The ratio of the total amount of isotope in the urine to its concentration in 1 cc. of plasma and the product of these values have been plotted since in other studies[6] these calculations have accentuated the differences between thyrotoxic, normal and myxedematous individuals. The clinical response during the first six months only is considered here because most of the subjects experienced a remission during this interval and because treatment beyond it was given more irregularly and was more complicated by repair processes in the thyroid gland.

Most of the thyrotoxic subjects who experienced a remission in six months received an average of from 60 to 90 µc. per Gm. of thyroid tissue per month, or a total of from 175 to 300 µc. per Gm. Those who remained thyrotoxic received comparable amounts.

2. *Daily Excretion of Radioiodine in Urine Following Therapeutic or Tracer Doses:* Determination of the quantity of radioiodine excreted during the first twenty-four hours following therapeutic doses showed (Fig. 4) in most instances that from 20 to 40 per cent of the dose was excreted. Comparison of these values with the quantities of isotope used in producing remission within six months revealed no definite correlation whether the dosage was expressed as total millicuries, total microcuries per Gm. of thyroid, or the average number of microcuries per Gm. of thyroid per month. Furthermore, in these cases there was no significant effect on the quantity of radioiodine in the urine when standard treatment with propylthiouracil was continued until two days before isotope therapy.

In the group of patients followed for several days (Fig. 5) the quantity of radioiodine in the urine decreased considerably after the first one or two days following therapy, when as much as 1 per cent of the initial dose continued to be excreted daily for many days. The quantity of isotope in the urine of one patient (Ch.) given three therapeutic doses showed relative increases, while in another subject (Bo.) there was less after the second treatment than after the first. One individual (Si.) given two equal-sized tracer doses within three weeks, without any therapy in the interim, excreted 18 per cent within twenty-four hours after the first dose and 13 per cent after the second dose. By the end of the fourth day the total excretion was the same in each instance. The subject who took propylthiouracil until the day of radioiodine administration excreted relatively the same amount of isotope as did the patients who had not

received this therapy. On the other hand, the subject taking potassium iodide excreted relatively more.

The quantity of radioiodine that was excreted during the intervals studied was a poor index of the total dose required to produce a remission. The patients who had diffuse goiters became euthyroid after receiving from 70 to 90 μc. per Gm. of thyroid per month; those with nodular goiters needed less per Gm. of tissue but a greater total quantity.

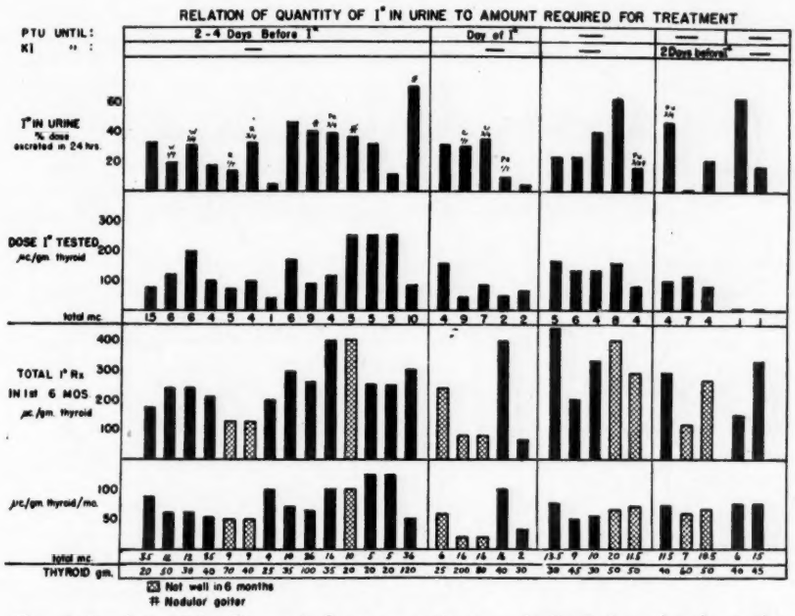

FIG. 4. See legend for Figure 3. In some patients, as indicated on the chart, the same test was conducted twice. For comparative purposes the patient's initial and the date of the test are included in the data. The weights of the thyroid are those estimated at the time of the first radioiodine treatment.

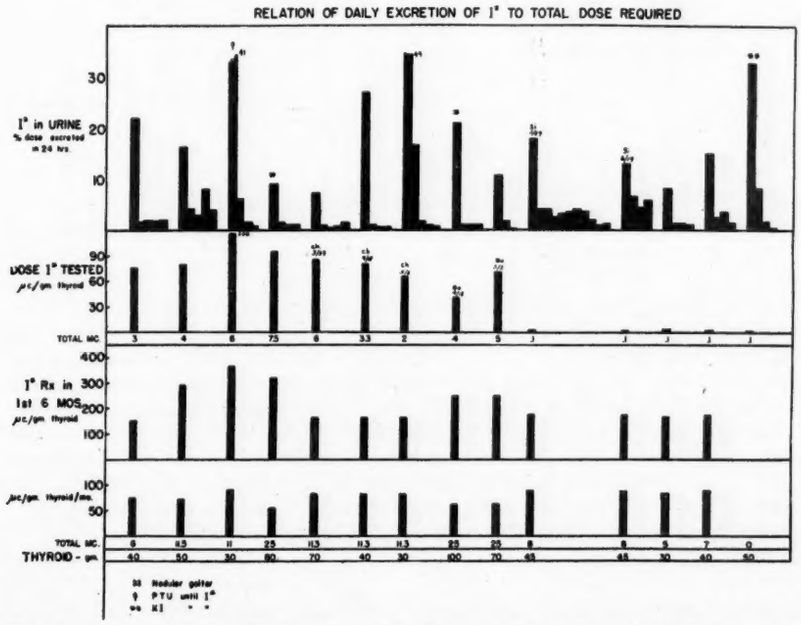

FIG. 5. See legends for Figures 3 and 4. Each of the patients included in this figure experienced a remission within six months and it has been sustained subsequently.

Relationship of the Physical Characteristics of the Thyroid Gland and the Intervals of Therapy to the Dosage Used to Produce Remission. There is no way of determining the minimal dosage required to produce a remission in a given patient but experience permits reasonable estimates. The results in patients with toxic nodular goiters indicate that in some instances, even after a state of euthyroidism is established, 10 mc. or more of radioiodine may be given without altering the metabolic rate. However, in some subjects with toxic diffuse goiter apparently a difference of 1 or 2 mc. in dosage will determine whether hyperthyroidism or euthyroidism will be produced; in other instances this same difference in dosage may determine whether euthyroidism or myxedema will develop.

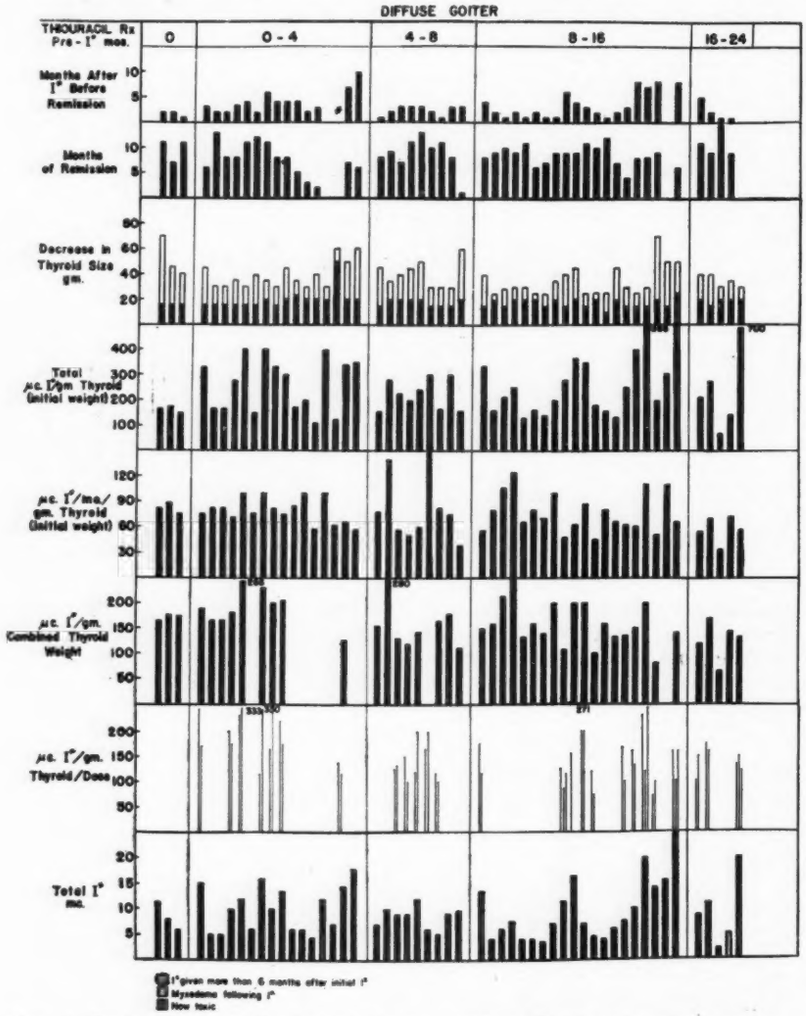

FIG. 6. Each column indicates data in one patient. In the top row is demonstrated the interval from the first dose of radioiodine until a remission was obtained that has been sustained. The present size of the thyroid glands is demonstrated by the black columns, while the blank portions of the columns show the extent to which they have decreased in size. The method and rationale of calculation of the μcI*/mo./gm. thyroid and the μcI*/gm. combined thyroid weight (or average thyroid weight) have been presented in the text. In the section labeled μcI*/gm. thyroid/dose are presented the data in patients given more than one radioiodine treatment within the first six months of therapy. One patient, indicated by #, did not return for additional therapy.

In Figure 6 are presented some of the results obtained in patients with toxic diffuse goiter. Because many patients had been treated with one of the thiouracils for

varying intervals and inasmuch as sustained remissions may follow such therapy, the cases are separated according to the intervals of previous treatment with these compounds. (Fig. 6.) In each patient it was clearly established that the individual was propylthiouracil was given immediately before the radioiodine but usually was stopped about four days before the latter.

It may be observed (Fig. 6) that all but two of the patients with diffuse goiters experienced remission of thyrotoxicosis.

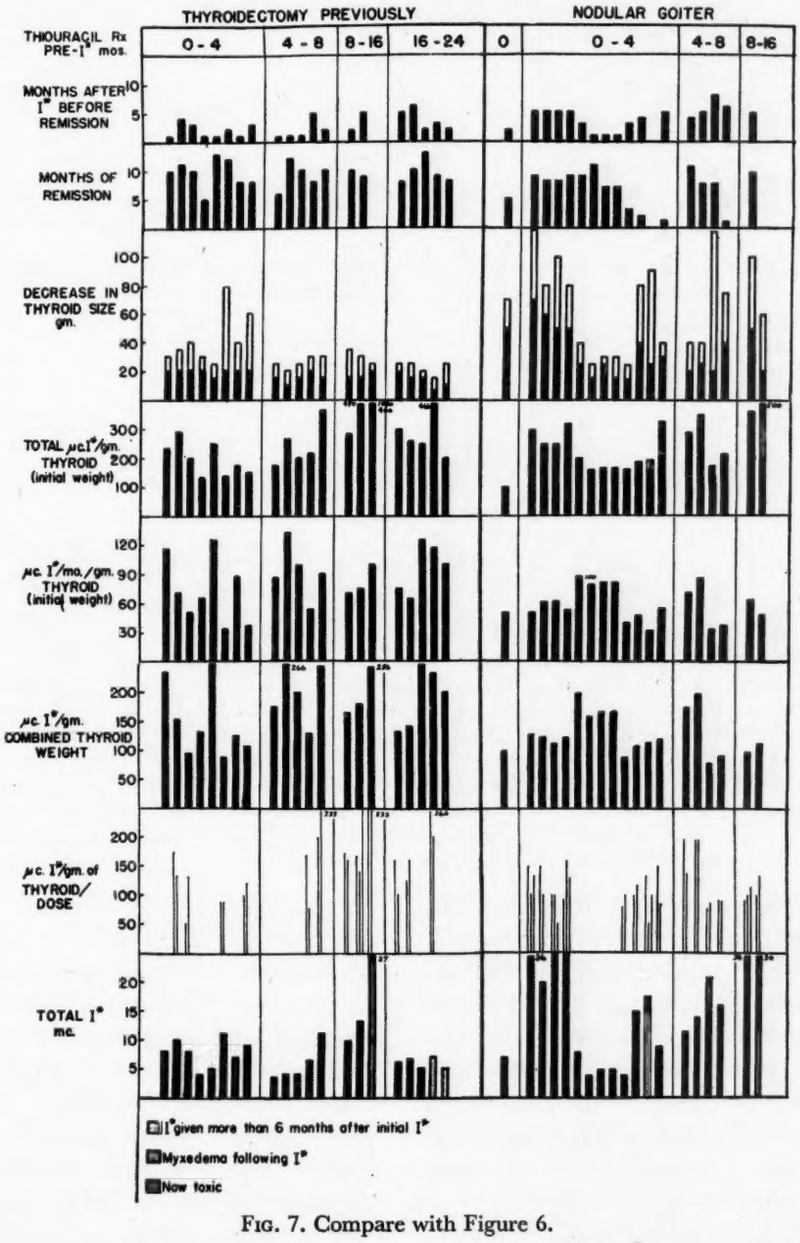

FIG. 7. Compare with Figure 6.

thyrotoxic when this therapy was withdrawn. Thus the radioiodine was not given immediately after long intervals of thiouracil treatment but was separated from it by one or more months. In some of these cases a short course, one to five weeks, of Moreover, in all but seven cases the remission occurred within six months. One subject developed myxedema. The thyroid in all patients decreased to 25 Gm. or less except in one who failed to return after the initial dose of radioiodine.

There is no statistically significant difference in the dosage of radioiodine used to produce remission in the groups of patients previously treated for varying intervals with thiouracil.[1] The patient (Fig. 6) who developed myxedema following radioiodine had had prolonged therapy with thiouracil; without thiouracil thyrotoxicosis reappeared, although of much milder degree. He received less radioiodine than the average quantity given to other patients. On the other hand, another individual who had taken thiouracil for more than two years and whose thyroid gland weighed approximately 30 Gm. has continued to have thyrotoxicosis after 20 mc.

Upon comparing Figures 6 and 7 it may be observed that there was no significant difference in the dosage used in the different groups when expressed upon a thyroid-weight basis. The total amount used in the subjects with toxic nodular goiters was greater than in those with diffuse goiter. Moreover, many of the nodular glands remained enlarged although remissions of the thyrotoxicosis developed. Two patients with nodular goiter have remained thyrotoxic in spite of 17.5 mc. in one case and 30 mc. in another. Two individuals who had had a thyroidectomy and had been treated with thiouracil for intervals of from sixteen to twenty-four months developed myxedema. Neither received as much as the average amount given to the other patients.

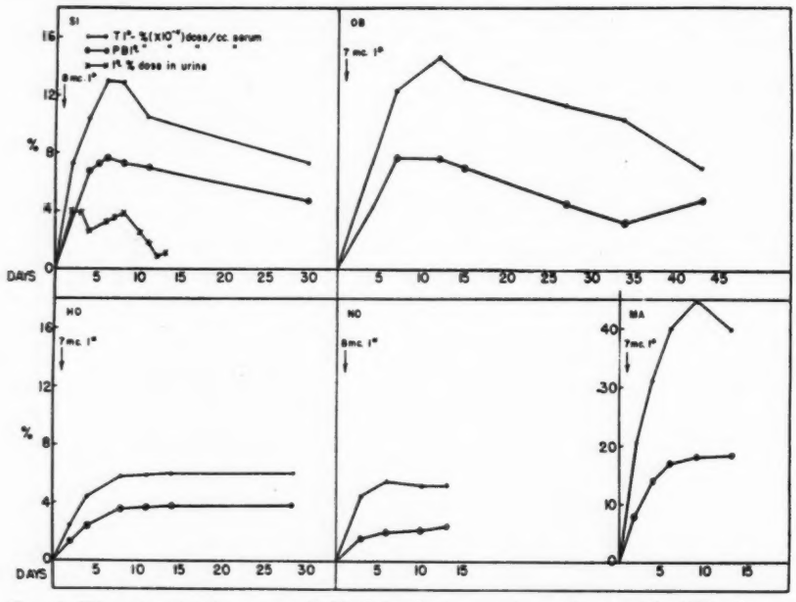

FIG. 8. The plots in the upper half of the figure are in patients with diffusely enlarged thyroids but the others were nodular. No. and Ma. had no thyrotoxicosis but the others were severely toxic. Each patient received 0.3 mg. KI with the radioiodine, but none received KI or PTU following it. No. received 50 J.S. units of thyrotropin in sesame oil for each of two days before I*. All of the thyrotoxic patients have had remissions which have now lasted for more than seven months. The diffusely enlarged glands decreased in weight from approximately 45 gm. to less than normal size (20 gm.); the nodular glands decreased only slightly. Following removal of Ma.'s gland several months later characteristics of a thyroid storm were observed, although repeated clinical examinations, including estimations of the basal metabolic rate, had shown no evidence of thyrotoxicosis.

Change in the Total and Protein-Bound Radioiodine Content of the Serum Following Therapeutic Doses. Aside from the usual factors which affect iodine metabolism, further changes are produced by radioactivity. As a result of the latter action a decreased rate of synthesis of PBI* and a relative increase in "spillage" of PBI* and PBI from the thyroid gland may be anticipated. The extent to which this "spillage" phenomenon takes place, with the increased metabolic rate which it may produce, may be expected to

effect the quantity of TI* and PBI* in the body.

Following the administration of therapeutic doses of radioiodine the changes in PBI* were determined in sixteen patients and the TI* in eleven for intervals of from two to six weeks. Fourteen of the patients had thyrotoxicosis; five of the fourteen had nodular goiters. Two individuals had nontoxic nodular goiters.

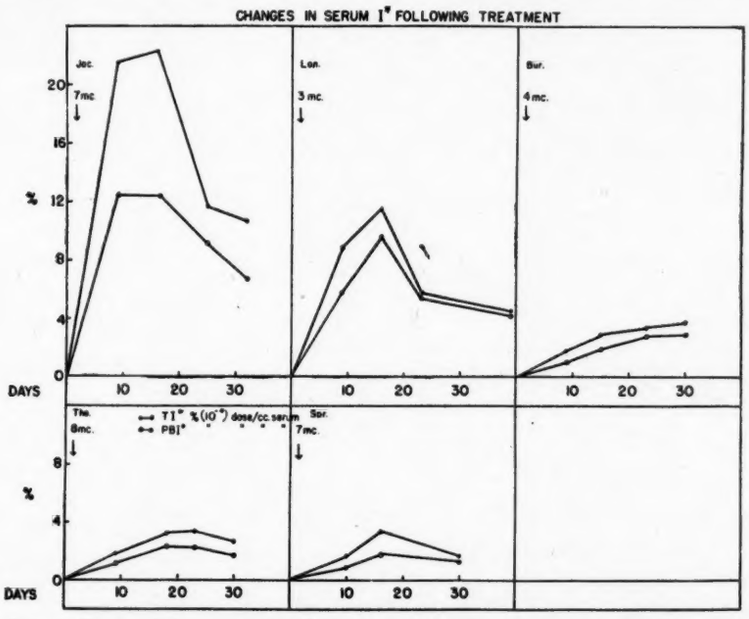

FIG. 9. Each of these patients had thyrotoxicosis; it was severe in Jac. and Tho. The thyroid was diffusely enlarged in Jac. and Lon. and was nodular in the others. Approximately 30 gm. of tissue were estimated to be present in Lon. and Bur. and 75 gm. in the others. The treatment of these patients was especially different from that of the patients in Figure 8 in that twelve hours after the radioiodine was administered each patient was given 3 drops of a saturated solution of potassium iodide and he continued to receive it twice daily for five days; it was then discontinued. Bur. and Spr. experienced remissions in thyrotoxicosis that have persisted for more than six months, but additional therapy was given to the others within six weeks.

The serum values and some of the characteristics of each case are given in Figures 8, 9 and 10. The subjects charted in Figure 9 were given potassium iodide for five days following radioiodine while those in Figure 8 were not. The increased quantity of iodine in the body would promote more rapid excretion of radioiodine. Since iodine tends to inactivate thyrotropin, one would anticipate that this therapy would cause a slower synthesis of PBI* but an increased tendency for its storage in the thyroid. Because iodine promotes a longer stay of radioiodine in the thyroid cells,[7] the resulting injurious effects on the cells would probably decrease the synthesis of PBI*. On the other hand, the injured tissue might permit a greater "spillage" into the blood stream of such PBI* as had been synthesized. As a final result of these effects of iodide a slower increase in the serum of TI* and PBI* might be anticipated with less of a total increase. However, a decreased rate of utilization of PBI* probably results as the metabolic rate decreases.

The maximal concentrations of PBI* were found between the fifth and twentieth days. During this interval there also tended to be the greatest difference between the concentration of TI* and PBI*. In each patient significant concentrations were found for as long as the patients were followed, which in one instance was six weeks. In no instance did the PBI* ever account for all of the TI* although these two values tended to approach each other after the

twentieth day. The TI* and the PBI* reached higher levels in the patients with diffuse goiter than in those with toxic nodular glands. In the latter group the rise in TI* and PBI* was slower; there was a more prolonged plateau, a slower fall and less of a difference in the TI* and PBI*.

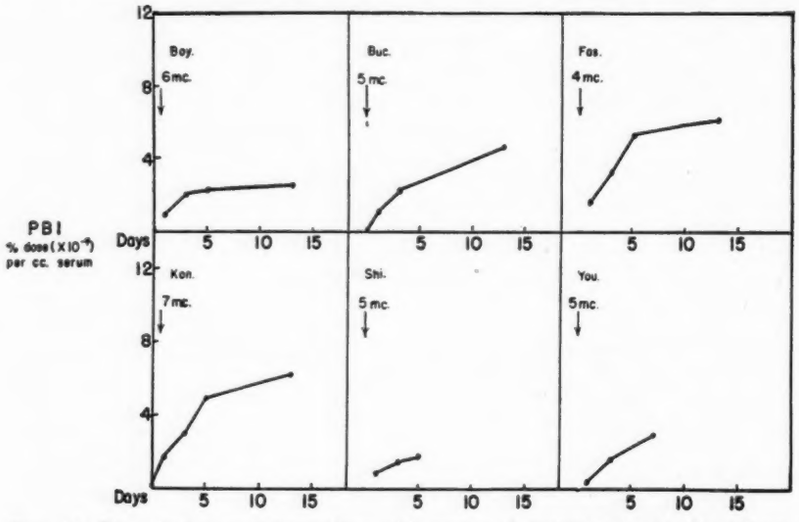

FIG. 10. Boy. had a nodular goiter with severe thyrotoxicosis; in the others the disease was less severe and the gland was diffusely enlarged. Potassium iodide therapy was like that given the patients described in Figure 8. The thyroid gland of Buc., Fas., Shi. and Kon. weighed approximately 30 gm. and decreased to less than 20 gm. within several weeks following radioiodine therapy. In Boy. the gland weighed 60 gm. before and after the therapy shown. Buc. developed myxedema; Fas., Shi. and You. have needed no more therapy; after 3 mc. of additional treatment Kon. experienced a remission.

The concentration in patient Ma. Fig. (8) became much greater than in any of the others. This subject had a nodular goiter which clinically was non-toxic but microscopically it appeared very active. This patient is unique in several respects and is being investigated further.

The nature of the plots in Figures 8, 9 and 10 does not indicate the efficacy of the therapy with reference either to the reduction in gland size or thyrotoxicity.

COMMENT

The effectiveness of radioiodine in the treatment of thyrotoxicosis is due to its capacity of injuring thyroid acinar cells, leading to disappearance of a large proportion of them. Its efficiency depends upon the amount and duration of exposure of the individual thyroid cells to ionizing radiation. The amount of radioactivity possessed by the isotope can be readily determined but its effectiveness in controlling thyrotoxicosis is dependent upon a large number of factors which modify its concentration and distribution in the thyroid. Apparently the metabolism of radioiodine is like that of iodine. Some of the factors influencing the distribution of the latter are discussed below.

Thyrotropin causes (1) an increase in the rate of transfer of thyroid hormone from the thyroid acini to serum, (2) a decrease in the storage of hormone in the thyroid gland, (3) hypertrophy and hyperplasia of the acinar cells, (4) an increase in the rate of transfer of iodide from the serum to the thyroid, (5) an increase in the rate of synthesis of the thyroid hormone and (6) an increase in the rate of transfer of iodine from the cells to the lumen of the acinus. The quantity of thyrotropin released is influenced, presumably, by many factors such as the quantity of iodine in the diet and amount of stress. Moreover, factors which affect its inactivation and excretion would also influence, indirectly, the exchange of iodine in the thyroid.

Iodine inactivates thyrotropin and tends

to inhibit its effects. Moreover, the quantity of iodine in the body may exert significant effects upon the exchange of radioiodine in the thyroid independent of its effects on the thyroid, for example, upon the serum; thyroid iodine gradient, excretion of iodine in the urine, etc. Among the factors affecting the quantity of iodine in the body are the amount ingested in food or as medicine and the quantity in water and in air. The quantity of iodine in the thyroid is influenced by the amount in the blood; antithyroid substances in the diet, thioureas, thiocyanates, etc.; thyrotropin activity and the structure of the thyroid. Of course, many of these effects are interdependent.

Results and Present Plan of Therapy. Some of the variables influencing response can be assessed following the administration of radioiodine by the determination of (1) the concentration of isotope in the thyroid region, (2) its excretion in the urine, (3) its concentration in the blood and (4) correlation of these observations with gland size and time. However, many factors must be considered in interpreting the data obtained. For example, following a tracer dose the concentration in the thyroid region can be used as an indication of the relative quantity of therapeutic dose of isotope which will accumulate in the same region when given under the same conditions. Likewise, by estimating the quantity of radioiodine in the blood and urine, it can be adduced that a significant portion of the remainder is in the thyroid gland.[8,9,10] However, such information does not indicate the variations in concentration which may occur from cell to cell nor indicate the variations in ratios of concentration in cells and colloid. Furthermore, it must be emphasized (1) that I^{131} continues to irradiate the gland for several weeks and (2) during this interval the radioiodine is passing in and out of the gland repeatedly. In this connection it should be noted that as the injury of the acinar cells occurs, changes probably occur to alter the exchange of iodine in the thyroid and, therefore, make it different from the changes indicated in the beginning by the tracer studies. Moreover, it seems likely that all thyroid acinar cells do not have the same degree of radiosensitivity and, consequently, the concentration of isotope in the cell is not an exact indicator of the extent of injury that will result in it.

In spite of the many variables which may interfere with accurate estimation of the dosage of radioiodine needed we are very much in favor of extending the types of tests that have already been applied, as well as searching for new tests, because determination of the dosage needed is by far the most important phase of radioiodotherapeusis. Perhaps more helpful information can be obtained by following the changes in the distribution of radioiodine for several weeks following its administration.

The regimen that was used most commonly in the treatment of our patients consists of (1) discontinuation of iodide therapy at least four weeks before radioiodine is to be given, (2) administration of propylthiouracil for approximately four weeks, ending four days before the administration of radioiodine, (3) the use of 0.5 mg. of potassium iodide twice daily, beginning within twelve to twenty-four hours after radioiodine and continuing for five days, (4) the administration of another dose of isotope approximately eight weeks later, if indicated. Of course, it is difficult to know the value of some of these measures but some reasons for their plausibility may be discussed.

Early in our experience[1] a few patients developed a distinct exacerbation in their condition within a few days following radioiodotherapeusis. These were individuals who had no previous therapy of any type for thyrotoxicosis. It was reasoned that radioiodine had altered thyroid physiology in a manner similar to thyroidectomy, except that there was not the degree of alarm reaction associated with the latter. After thyroidectomy thyroglobulin can be found in the blood almost immediately thereafter and thyroid storm is most apt to occur in the first twenty-four hours. Although estimations of thyroglobulin following radio-

iodine have not been reported, it seems very probable that with the necrosis of the thyroid tissue resulting from irradiation thyroglobulin could enter the blood stream just as it has been shown[11] to do in patients with thyroiditis. An appreciable amount of necrosis would not be expected for several days and the maximal intensity of the exacerbation in thyrotoxicity requires a similar interval. Apparently, with radioiodine or by surgery, the release of significant amounts of thyroid hormone into the blood stream of a patient who already has a relatively high concentration and is in poor general nutritional state may lead to a thyroid storm. On the other hand, when such patients are treated adequately for several weeks with propylthiouracil, a decreased concentration of hormone results in the thyroid and other portions of the body together with an improved nutritional status; therefore, they are less subject to untoward reactions. In some instances propylthiouracil is given for intervals longer than four weeks and sometimes less, depending upon the severity of the thyrotoxicosis, the interval before the next expected shipment of radioiodine, etc. Propylthiouracil not only has this advantage but it promotes improvement in the patient while waiting for the isotope. Moreover, it probably increases the uptake of the radioiodine by the thyroid if discontinued four days before the latter. Essentially all of the drug disappears from the body during this interval. If it is given until the day of the iodotherapy, it may interfere with the uptake of iodine by the thyroid.

The extent to which propylthiouracil interferes is small compared to the effects of therapeutic doses of potassium iodide. Although this substance probably does not cause significant interference for as long as four weeks after cessation of its administration, there are enough variables of other types to make it desirable to remove any that are not necessary. The use of propylthiouracil preceding radioiodine therapy helps eliminate excesses of iodine in the body. Whereas statistically significant differences were not found, we have the impression based upon careful consideration of individual cases that patients previously treated for long intervals with thiouracil, or previously subjected to thyroidectomy or both, require relatively less radioiodine than patients not so treated.

Young patients were not given as large doses initially as adults, as we particularly desired to avoid myxedema in this group. We attempted to select the minimal dose which we thought might produce a remission, realizing that it was easier to give additional doses than to treat myxedema. A rule-of-thumb* which evolved for application in the selection of the initial dosage for a great proportion of patients with diffuse hyperplasia was as follows: 4 mc. if the gland weighed 30 Gm., and 1.5 mc. extra for each additional 10 Gm. in weight. Of course, as discussed at length, there are many factors modifying the dosage required.

The use of the carrier doses of iodide was based upon the work of earlier investigations.[2] On the basis of our clinical studies we could not detect a definite difference in response whether we gave potassium iodide, sodium bromide or nothing with the radioiodide. It was difficult to evaluate the influence of potassium iodide upon the effectiveness of radioiodine when given for five days after the latter. Whereas such a procedure tends to promote excretion of radioiodine and from this point of view would decrease its effectiveness, potassium iodide helps trap the isotope in the thyroid cells[7] which is where it is most desired. Whether or not this phenomenon is actually advantageous, iodide for a few days does help prevent exacerbations of the thyrotoxicity. Moreover, using it in the manner described apparently does not interfere significantly with interpretation of the effectiveness of radioiodine or in the next treatment with it.

The problem of when to give additional doses of radioiodine ranked next in difficulty

* This "rule-of-thumb," like so many others, probably will not hold very long but when applied to a limited group of patients it may be of aid for a while.

to the selection of dosage. In our earlier experiences we sometimes erred by repeating the treatment within four or five weeks. Now, with only few exceptions, we do not repeat the therapy within intervals less than approximately eight weeks. The interval required for patients to obtain a maximal response from a dose of radioiodine varies from one to five months. In general, patients who had had no definite response in six weeks or those who had had the maximal improvement after about four weeks and were experiencing an intensification of the manifestations by the sixth week invariably needed more therapy. The patients who were very mildly toxic by the end of eight weeks were followed for another two to four weeks before decision regarding additional therapy was made. Most of the patients who did not require additional therapy became euthyroid or hypothyroid within five to ten weeks. Patients who became myxedematous required three months or more to develop this picture. A few patients required three or four months to exhibit the maximal response to a given treatment although they did not develop myxedema. To illustrate the relative interval required for different degrees of response, the following "rule-of-thumb" may be stated: the maximal response in metabolic rate occurs within one month when treatment is inadequate, within two months when it is adequate and within three months when it is excessive. Of course there are notable exceptions to these generalizations.

The interval between the time of administration of radioiodine and remission of thyrotoxicosis is required not only to produce injurious effects on the thyroid cells but also to utilize the excess of hormone that had been manufactured previously. Since there is considerable variation in these respects, it is not surprising that the degree of response differs. For example, these factors are probably major ones in accounting for the slower response in metabolic rate of patients with toxic nodular goiter than in those with toxic diffuse goiter, while it was more rapid in those previously thyroidectomized. The greater variation in the physiologic and anatomic status of the thyroid of patients with nodular goiters than those with diffuse hyperplasia contributes to the greater irregularity in response. The fact that none of the former group developed hypothyroidism, although relatively large doses of radioiodine were given when the patients were euthyroid, can be attributed at least partially to the greater variation in the physiologic activity of the thyroid cells.

SUMMARY

In our experience with radioiodine in the treatment of 111 patients with thyrotoxicosis the quantity of isotope required to produce remission varied considerably.

In investigating technics that might be used as indicators of the amount of isotope needed, we attempted to correlate the dosage of isotope used with (1) earlier estimations of amounts of it in blood, urine or thyroid region after specific intervals and (2) clinical examination of the thyroid gland.

None of the methods was very satisfactory. Clinical evaluation of the thyroid gland was of moderate aid. Nodular goiters required larger total amounts of isotope than diffuse goiters but less per Gm. of thyroid. Previous therapy with thiouracils for long intervals or with thyroidectomy did show statistically significant differences in the quantity of radioiodine needed, except insofar as they affected the quantity of thyroid tissue present.

The value of the administration for short intervals of propylthiouracil before, and of potassium iodide after radioiodotherapeusis is discussed along with many other factors affecting the results of therapy.

REFERENCES

1. Williams, R. H., Jaffe, H., Towery, B. T., Rogers, W. F. and Tagnon, R. Radioiodotherapeusis. *Am. J. Med.*, 7: 702, 1949.
2. Hertz, S. and Roberts, A. The use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.*, 131: 81, 1946.
3. Chapman, E. M. and Evans, R. D. Treatment of

hyperthyroidism with radioactive iodine. *J. A. M. A.*, 136: 86, 1946.

4. LEBLOND, C. P. Localization of newly administered iodine in the thyroid gland as indicated by radioiodine. *J. Anat.*, 77: 149, 1943.
5. WILLIAMS, R. H., JAFFE, H. and KEMP, C. Effect of severe stress upon thyroid function. (To be published.)
6. WILLIAMS, R. H., JAFFE, H. and BERNSTEIN, B. Comparisons of the distribution of radioactive iodine in serum and blood in different levels of thyroid function. (To be published.)
7. LEBLOND, C. P. Presented before the Laurentian Hormone Conference, St. Adele, Quebec, September, 1947.
8. HAMILTON, J. G. and SOLEY, M. H. Studies in iodine metabolism by the use of a new radioactive isotope of iodine. *Am. J. Physiol.*, 127: 557, 1939.
9. HAMILTON, J. G. and SOLEY, M. H. Studies in iodine metabolism of thyroid gland in situ by use of radioiodine in normal subjects and in patients with various types of goiters. *Am. J. Physiol.*, 131: 135, 1940.
10. HERTZ, S., ROBERTS, A. and SALTER, W. T. Radioactive iodine as an indicator in thyroid physiology. *J. Clin. Investigation*, 21: 25, 1942.
11. LERMAN, J. Iodine components of blood. Circulating thyroglobulin in normal persons and in persons with thyroid diseases. *J. Clin. Investigation*, 19: 555, 1940.

Radioactive Iodine, I-131, in the Treatment of Hyperthyroidism*

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RADIOACTIVE iodine (I^{131} eight day half-life) is an agent for the treatment of toxic goiter which has been studied at the Presbyterian Hospital for the past three years. The present report summarizes our experience in 103 patients.

When this work was initiated, information concerning dosage was scant.[1,2] Hence the first patients were treated more or less empirically. On the basis of known physical data and from previous experience with x-ray therapy it was calculated that a dose of 3 to 4 millicuries of I^{131} would deliver a satisfactory irradiation to a moderate sized thyroid. It was soon noted that failure to respond to this dosage occurred mostly in patients with initially large glands and in those markedly thyrotoxic.[3] A second dose of 3 to 4 mc. was given to most of these patients four months after the initial treatment but with no better response.[4] By January, 1948, the accumulated data indicated that about 50 to 100 μc. I^{131} retained per estimated Gm. of thyroid tissue resulted in satisfactory remission in a high percentage of cases.[5] Since the average retention of I^{131} after ingestion is about 50 per cent of the administered amount, the administration of approximately 100 to 200 μc. per estimated Gm. of gland weight would approach the desired goal. A total dosage of about 3 to 15 mc. would thus be required. However, for fear of inducing a high incidence of hypothyroidism it was decided to limit the highest dosage to 6.5 mc. and to retain the lower limit at 3 mc. Larger glands accordingly received somewhat less than the desired amount of I^{131} per Gm. of gland tissue and smaller ones somewhat more. Those patients failing to show remission within four months on such dosage were retreated. A final third dose was given to the few patients who remained uncontrolled four months later.

Forty patients were treated prior to January, 1948, and sixty-three patients from then to February, 1949, with a follow-up period of from almost three years to a minimum of at least four months. The results obtained indicated considerable success in inducing remission of hyperthyroidism by means of radioiodine (I^{131}).

METHODS

The earlier methods of Hertz,[1] Hamilton and Soley[2] and others[6,7] for radioiodine therapy in hyperthyroidism have been reported. The relative merits of I^{130} (twelve hour half-life) and I^{131} (eight day half-life) have been discussed.[8] At the present time, with I^{131} readily available from the atomic pile at Oak Ridge, the shorter-lived isotope no longer is employed. I^{131} was made available by the Atomic Energy Commission for investigative use in September, 1946. Since then the material has been obtainable in relatively large quantities, at low cost and essentially carrier-free (that is, not mixed with stable iodine). This last specification is important since it insures against the production of unwanted biologic effects due to iodine *per se*, as opposed to the desired radiation effects resulting from the gradual breakdown of the radioiodine.

Adequate arrangements are necessary for the safe handling of iostopes to avoid radiation dangers. The establishment and maintenance

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of these precautions was made the responsibility of a health officer. There were a number of problems connected with the clinical use of radioiodine. These included handling the isotope prior to its administration to the patient and the subsequent proper disposal of the patient's excreta. The avoidance of irradiation of other individuals from the material in the patient had to be considered although this hazard is generally not incurred to a significant extent in the treatment of hyperthyroidism. These problems have been discussed in detail elsewhere.[9]

The subject of radioiodine standardization has been the source of considerable confusion. "Millicuries," as reported in the literature, may represent widely discrepant values.[10] All clinics in New York City have for two years employed a "New York millicurie" (corresponding, fortunately, to the one already employed in this clinic). This unit is about 1.4 times as great as the millicurie used by Oak Ridge until July 1, 1949, and is within 10 per cent of the unit now in use there. All doses herein reported are in terms of the New York millicurie.

The desired amount of I^{131} for either tracer or therapeutic use is diluted in water for ingestion by the patient. The container is then carefully rinsed and the washings also swallowed to insure against loss of activity. The patient need not be in the fasting state unless the rate of accumulation of radioiodine in the thyroid[11] is being studied. Twenty-four hours after ingestion of the I^{131} the uptake by the thyroid is measured.[12] At this point uptake is usually maximal and tends to reach a plateau.

Per cent uptake is determined by direct measurement over the thyroid gland with the Geiger counter. Necessary precautions in making such measurements have been discussed in detail elsewhere.[9] It is sufficient to point out here that the counter must be at a great enough distance and have a large enough aperture so that radiation from the entire gland is measured. Approximation of thyroid uptake from urinary excretion is definitely less satisfactory[13,14] and has been used at the Presbyterian Hospital only to supplement uptake studies.

Knowledge of I^{131} uptake by the thyroid is important in calculating radiation delivered to the gland. The radiation delivered to the thyroid depends both on the amount of I^{131} deposited per Gm. of gland tissue and its rate of biologic elimination due to secretion as iodine-containing hormone. The formula for calculating dosage is:

$$\text{Equivalent roentgens (e.r.)} = \frac{\text{mc. administered} \times \%\ \text{uptake}}{\text{gland weight}} \times \text{effective half life} \times 160.$$

The term "equivalent roentgen" has been devised to include both beta and gamma ray dosage since the "roentgen" properly applies only to X and gamma rays. For practical evaluation of dosage the roentgen and equivalent roentgen may be considered to be the same. The magnitude of the equivalent roentgen (e.r.) is essentially the same as that of the "rep" used by some workers.

The determination of gland weight as used in the dosage formula is admittedly the least accurate part of the calculation. Gland size can be only roughly approximated. The practice of this clinic has been to rely on the results of palpation carried out by the same individual (S. C. W.) in all cases. Subsequent comparison of these estimates with a series of plasticine models representative of varying sizes of the thyroid is then made as an aid in classification.[3] Soley, after comparing his own estimates of gland size from palpation with those made from specimens obtained subsequently at operation, calculated a discrepancy of about 30 per cent between the two.[15] This agrees with our own approximation of error involved.

The term "effective half life" in the dosage formula above is used to express the deviation from the physical half life of eight days which results from the gradual loss of radioiodine from the gland as hormone secretion. If this elimination or secretion did not occur, the isotope would remain in the gland for total decay, delivering its radiation at a rate determined by its eight day half-life. Actually, half the original amount of isotope taken up by the gland is found at between four and seven days, with an average age of six days. This shorter "effective half life" establishes the actual rate of radiation. This "effective half life" has to be determined experimentally for each individual patient by making weekly measurements of thyroid gland radioiodine content and plotting the disappearance rate.

The factor 160 in the formula is the calculated radiation in equivalent roentgens when one microcurie of I^{131} remains in 1 Gm. of tissue for total decay. This number depends on the disin-

tegration scheme of the isotope, the energy of the liberated radiations and their absorption coefficients in tissue.[16] Thus the entire formula takes into account the number of microcuries deposited per Gm. of estimated gland tissue, and the "effective half life" as a correction factor to the theoretic dose calculated from the physical half life of the I^{131}.

The selection of cases for therapy was influenced by several factors. The diagnosis of toxic goiter was clear-cut and uncomplicated in all instances and was confirmed by repeated determinations of basal metabolic rate and of fasting serum cholesterol, and more recently by measurement of tracer uptake of radioiodine[12] and of serum precipitable iodine.[17] However, after January, 1948, an effort was made to select patients with large glands and high toxicity of hyperthyroidism. Primary unoperated toxic goiter and toxic goiter recurrent after operation were accepted for therapy but toxic nodular goiter was avoided. No patient was accepted for therapy under twenty-three years of age, except in two instances.

CLINICAL DATA

The patients in the present study are classified into two groups, those treated prior to January 1948 and those treated from then to February 1949. An analysis has been made of each group separately and of the combined experience.

Series I. Patients Treated October, 1946, to January, 1948. This series numbered forty patients. There were twelve men and twenty-eight women. Ages ranged from eighteen to sixty-three. Twenty-four of the patients had unoperated primary toxic goiter; sixteen had a recurrence of toxicity after previous surgery. Protracted antithyroid drug therapy had been given without production of permanent remission to six cases.

The results of a single dose of 3 to 4 mc. I^{131} are presented in Table I. Approximately two of three patients responded to a single dose. Two were operated because it was believed unwise to delay definitive treatment and the rest were treated a second time. Retreatment was given only if remission was not observed at follow-up four months after the initial dose. Retreatment brought the total number of remissions to thirty-three (84.6 per cent) with four more failures. One patient was lost to follow-up.

Series II. Patients Treated January, 1948 to February, 1949. This group numbered sixty-three patients. There were twelve men and fifty-one women. Ages ranged from seventeen to sixty-eight. Forty-four of the patients had previously unoperated primary toxic goiter and nineteen had toxicity recurrent after surgery. Prophylthiouracil had been given over long periods without induction of permanent remission in thirteen cases.

TABLE I
RESULTS OF TREATMENT OF TOXIC GOITER WITH RADIOIODINE I^{131}
October 1, 1946–January 15, 1948

Total number of patients 40
Primary toxic goiter 24
Recurrent 16
Dosage ..... 3–4 mc.

	No.	Per Cent
Results after 1 dose only		
Remission	29	72.5
Failure	2	5.0
Retreated	9	22.5
Hypothyroid	0	0.0
Results after 1st and 2nd doses		
Remission	33	84.6
Failure	6	15.4
Hypothyroid	0	0.0
Lost to follow-up	1	

The results of a single dosage of 3 to 6.5 mc. is shown in Table II, the size of dose given bearing a more or less direct relation to the size of the gland and toxicity of the disorder. Of the sixty-three patients in this group thirty-six were put into remission by a single treatment, one was believed too sick to warrant further uncertainty and was operated upon, two were lost to follow-up, three were made permanently hypothyroid and twenty-one were retreated. Retreatment was not given before three to four months following the initial dose. The dosage range for retreatment was the same as originally given, 3 to 6.5 mc., although in any given patient a smaller gland and decline in toxicity frequently permitted the use of smaller dosage than initially used.

The total brought into remission after one or two treatments was forty-eight (81.3 per cent). One more patient was now considered too ill to delay definitive therapy with surgery and no others were lost to follow-up. No additional patients were made hypothyroid. A third treatment with 3 to 6.5 mc. was given to the five patients still toxic, again not until at least three or four months had passed from the time of the second dosage. Following this final effort the final number of cases in remission was fifty-two (89.6 per cent); four (6.9 per cent) hypothyroid, and in all, two (3.4 per cent) failures. Thus, about 95 per cent of the patients in this group were relieved of toxicity.

TABLE II
RESULTS OF TREATMENT OF TOXIC GOITER
January 15, 1948–May 15, 1949

Total number of patients..... 63
Primary toxic goiter..... 44
Recurrent toxic goiter..... 19
Average BMR..... +40%
Dosage..... 3–6.5 mc.

	No.	Per Cent
Results after 1 dose only		
Remission	36	59.0
Failure	1	
Retreated	21	36.1
Hypothyroid	3	5.0
Lost to follow-up	2	
Results after 1st and 2nd doses		
Remission	48	81.3
Failure	2	
Retreated	5	
Hypothyroid	3	
Under observation (probable remission)	2	
Results after 1st, 2nd and 3rd doses		
Remission	52	89.6
Failure	2	3.4
Hypothyroid	4	6.9
Under observation (probable remission)	3	
Lost to follow-up	2	
Euthyroid and hypothyroid	56	96.5

Total Series. A summary of the total experience is shown in Table III. There were 103 cases. Twenty-four were men and seventy-nine were women. Ages ranged from seventeen to sixty-eight. Sixty-eight represent primary toxic goiter; thirty-five had toxicity recurrent after surgery. The basal metabolic rate ranged from +12 to +76 per cent, with well over 85 per cent of the values higher than +20 per cent. The figures for treatment with an initial dose of between 3 to 6.5 mc. show sixty-five (61.3 per cent) remission, three (3 per cent) hypothyroids, three (3 per cent) failures and three lost to follow-up. The results of the second and third doses are shown in Table III. The cumulative effect of the treatments show eighty-five (87.6 per cent) in remission, four (4.1 per cent) hypothyroid, eight (8.2 per cent) failures and three lost to follow-up. Three patients are still under observation. The total relieved of hyperthyroidism and either euthyroid or hypothyroid is eighty-nine (91.7 per cent).

TABLE III
RESULTS OF TREATMENT OF TOXIC GOITER
October 1, 1946–May 15, 1948

Total number of patients..... 103
Primary toxic goiter..... 68
Recurrent toxic goiter..... 35
Dosage..... 3–6.5 mc.

	No.	Per Cent
Results after 1–3 treatments		
Remission	85	87.6
Failure	8	8.2
Hypothyroid	4	4.1
Euthyroid and hypothyroid	89	91.7
Under observation	3	
Lost to follow-up	3	

Analysis of Results from an Initial Dose of I^{131}

Series I. An analysis of the failures in this group has been reported before.[3,4] Large glands inevitably receive less radiation than small ones when a constant dosage of I^{131} is used. The results in this group suggested that dosages of 100/200 μc/estimated Gm. gland of tissue and a radiation greater than 5,000 e.r. gave the best insurance of success. Gland size was noted to have returned to normal in almost every instance of successful therapy but

enlargement generally persisted in the case of failure.

Series II. This group was treated with varying dosage in an attempt to provide 100–200 μc. per estimated Gm. of tissue and thus approximate 5,000 e.r. as suggested by

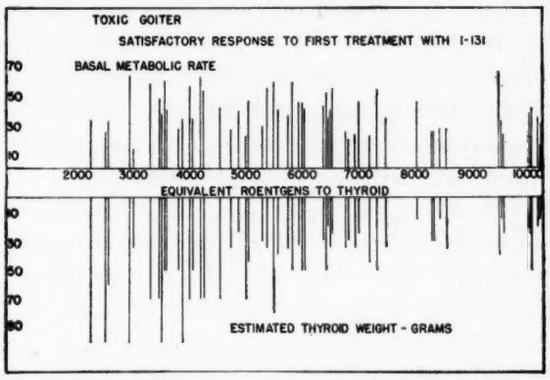

FIG. 1. Graph showing basal metabolic rate and gland size before I^{131} therapy and total radiation received in patients entering remission after a single treatment.

the analysis of results from Series I. A limit of 6.5 mc. was set, however, despite gland size (see "Methods").

TABLE IV
TABLE OF DOSAGE RANGE TREATMENTS SINCE JANUARY 15, 1948

Dose	Remission	Failure
6.5 mc.	0	1
6.0	6	1
5.5	7	2
5.0	18	5
4.5	9	2
4.0	9	13
3.5	7	1
3.0	3	3

The successful and unsuccessful results of a single dose of I^{131} in this second series have been correlated with the dosage per estimated Gm. of gland tissue and with the radiation received by the entire thyroid. (Tables IV to VI; Figs. 1 and 2.) It is readily seen that the initial goal of dosage was only roughly achieved and that an even wider range of radiation resulted. The variability in gland uptake and in "effective" half life accounts for much of the latter. It is evident that there is no great difference in the dosage per estimated Gm. of gland or radiation received between those patients brought into remission or those representing failure of treatment.

Gland size almost uniformly returned to normal with remission and not with failure. However, gland size was not entirely reduced in 8 per cent of successfully treated patients.

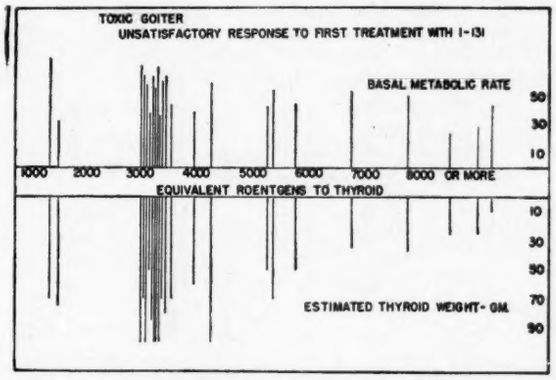

FIG. 2. Graph showing basal metabolic rate and gland size before I^{131} therapy and total radiation received in patients not entering remission after a single treatment.

TABLE V
TABLE OF DOSAGE PER ESTIMATED GM. OF GLAND WEIGHT TREATMENTS SINCE JANUARY 15, 1948

Dose/Estimated Gm.	Remission	Failure
300–349	1	0
250–299	3	1
200–249	4	1
150–199	5	4
100–149	22	6
50– 99	22	16
0– 49	1	1

TABLE VI
TABLE OF EQUIVALENT ROENTGENS TREATMENTS SINCE JANUARY 15, 1948

E.R.	Remission	Failure
10,000 up	5	3
9,000–9,900	3	1
8,000–8,900	6	1
7,000–7,900	5	1
6,000–6,900	10	6
5,000–5,900	9	5
4,000–4,900	8	5
3,000–3,900	8	4
2,000–2,900	4	1
1,000–1,900	1	1

Complications after I^{131} Therapy

The incidence of major complications following I^{131} therapy in the series of patients treated since January, 1948, is shown in Table VII.

Hypothyroidism. No critical level of dosage was found at which hypothyroidism could be avoided and remission of toxicity insured. Permanent hypothyroidism occurred at 11,800, 8,200, 7,700, 2,690 e.r. and with 230, 110, 65, 35 μc/estimated Gm. of gland tissue. Hypothyroidism, clinically evident and with appropriate laboratory findings, occurred transiently about the third month after therapy and cleared by the fourth month or so in seven patients given a wide range of dosage and of radiation. However, one patient still hypothyroid six months after I^{131} dosage was given thyroid orally for the next six months and was found to have regained normal thyroid function upon stopping thyroid medication.

TABLE VII

TABLE SHOWING INCIDENCE OF MAJOR COMPLICATIONS FOLLOWING I^{131} TREATMENT, SINCE JANUARY 15, 1948

Hypothyroidism	
Permanent	4
Transient	3
Diplopia and orbital edema	2
Heart failure after therapy	1

Thyroiditis. Tenderness and pain over the thyroid in the first few weeks after therapy occurred in three instances. However, a very firm feel to the gland may be noted in most instances one month after therapy, giving way to a softer consistency as the gland decreases in size. It becomes normal in consistency usually by four months after therapy, if still palpable.

Tracheitis and Laryngitis. Cough and hoarseness of the voice was noted in the first series of cases but not in the second group. The reason for this discrepancy is not clear.

Parathyroid Tetany. No instance of injury to the parathyroids was noted, clinically.

Exophthalmos. Care was taken to avoid cases suggestive of thyrotrophic, malignant, ophthalmoplegic exophthalmos. Significant advance in exophthalmos was observed in only two instances and occurred by the first month after therapy. It was associated with diplopia and mild chemosis. Treatment with desiccated thyroid was instituted in each instance with arrest of the eye changes, if not actual improvement, although whether this was coincidental or was cause and effect is not apparent.

Transient Exacerbation of Toxicity. A flare-up in toxicity, exactly similar to that seen after x-ray therapy, has been observed. The serum precipitable iodine was studied[18,19] and could be shown to rise concurrent with this exacerbation of hyperthyroidism.

Heart Failure. The appearance of heart failure as a result of flare-up of toxicity has not been observed. However, one patient developed heart failure during the first eight months of unsuccessful dosage but refused surgery and was finally controlled by a third dose of I^{131}. Two patients with heart failure have been treated successfully with I^{131}.

COMMENT AND CONCLUSIONS

It is clear that internal radiation with I^{131} offers a simple, highly effective method of treating toxic goiter. The results have been consistently good in all series so far reported[5,15,20–24] and enough patients have been treated to permit a sound appraisal. I^{131} therapy has one great advantage over surgery. It avoids the severe complications which occasionally result from operation, such as recurrent laryngeal nerve injury and tetany. It has the disadvantage that an average of six to eight weeks may elapse from the time of treatment until remission is induced during which time the patient continues to be toxic. Also, an initial dosage does not insure a greater than two in three chance of remission. Thus, a second or third treatment may be necessary, each time with several more months of persistent toxicity although this generally becomes progressively milder with each dose. These objections to I^{131} therapy are, however, relatively minor. Most patients would undoubtedly be treated in this way were there not another and major obstacle to its general application. It is feared by some that later malignancy may be induced in the thyroid as a

result of the effects of a radioactive agent. It has been shown by radioautography[25] that there is an irregular collection of the isotope within the thyroid gland following administration. This has suggested that some cells may receive disproportionate and undue radiation during radioiodine therapy. This uneven radiation, it is held, makes it likely that malignant degeneration in the gland may appear fifteen to twenty years hence.

On the other hand, such malignant change has not apparently been noted following this interval after external radiation therapy of the gland by x-rays.[26] Moreover, as pointed out by Dr. Robley Evans,[27] it is generally a chronic radiation of low intensity which is associated with the development of later malignant change and not the brief and much more intense radiation provided by I^{131}. Despite these arguments in favor of and against the likelihood of later malignancy following I^{131} therapy, the issue has not been settled and remains conjectural. One approach to the problem has been to limit treatment of uncomplicated toxic goiter, with I^{131} to patients in the older age groups, forty-five years or over.[24] Survival much beyond twenty years is unlikely and hence the seriousness of later cancer formation is greatly minimized. This program allows for continued experience with the isotope and permits definitive therapy of the complicated case, such as the cardiac in whom surgery is inadvisable. However, rigid restriction to the age limit of forty-five is probably inadvisable. The younger patient who refuses surgery, or is not suitable for it and who is not brought into remission by external radiation or chronic therapy with antithyroid drugs probably should be given the benefit of I^{131} since this method will almost certainly induce remission. On the other hand, the adolescent age group and younger, i.e., from about age twenty, probably should not be treated under any circumstance in the present state of knowledge.

The above discussion holds for primary, previously unoperated toxic goiter. The problem of radioiodine therapy for toxic goiter recurrent after operation is different. Here, unlike the situation with primary hyperthyroidism, a marked superiority of therapy with I^{131} over surgery has been demonstrated. Moreover, the other methods of treating primary goiter are found to be far less effective in the instance of recurrent hyperthyroidism than they are in the previously unoperated disease. Thus recurrent toxic goiter probably should be treated by preference with I^{131} since its greater efficacy would appear to outweigh the theoretic objections to its use.

To establish this point a rough comparison of the results after I^{131} with those after other modalities is presented. Radioiodine apparently produces the same 90 per cent ultimate remission rate in recurrent toxic goiter as it does in primary hyperthyroidism. This plus a 7 per cent incidence of hypothyroidism makes a total of 97 per cent of hyperthyroid patients relieved of toxicity, whether recurrent or not. A second surgical procedure on the other hand, once toxicity has recurred, is generally conceded to be only about 50 per cent effective, while a third operation is perhaps even less effective.[28] This is apart from the sharply increased technical difficulty of reoperation and the added risk of serious complications such as injury to the recurrent laryngeal nerve and parathyroid glands, and other well recognized complications.

The reports concerning external radiation with x-ray have not been specifically analyzed for its effectiveness in recurrent toxic goiter. However, everyday experience indicates that the efficacy of the method in recurrent goiter is not better than the 60 to 80 per cent remission rate achieved in primary unoperated toxic goiter[29,30] and appears to be even less. Protracted therapy with antithyroid drugs is surprisingly ineffective in recurrent toxic goiter and is considerably less than the 40 to 60 per cent remission rate generally obtained in the previously unoperated group.[31,32]

There is no apparent dividing line in amount of administered dosage, dosage per

estimated Gm. of gland weight, or radiation received by the gland which distinguishes successful therapy from failure. There is considerable overlap in the distribution curves of all these factors for those patients entering remission and those failing to do so. It is nevertheless a fair generalization that patients with high toxicity and large glands usually require larger initial as well as total dosage than do those with lesser toxicity and smaller glands. Similarly the amount of dosage and of radiation which will prevent hypothyroidism cannot be defined.

What the factors are which condition gland tissue responsiveness to internal radiation have not been completely elaborated. Presumably vascularity and distribution of colloid play an important role. The over-all result after such therapy is gland shrinkage and subsequent fibrosis although this may be surprisingly little for the first year after treatment.[33]

Since the efficacy of I^{131} therapeutically is dependent upon an adequate uptake of the isotope by the thyroid, agents blocking such uptake must be avoided. Thus antecedent stable iodine whether administered as sodium iodide or Lugol's solution or as an organic iodine compound during intravenous pyelography or with gallbladder dye will block iodine uptake.[12] In general, two weeks without stable iodine after brief periods of such therapy, or four weeks following more prolonged administration, will suffice to permit I^{131} to be given successfully. Similarly, preceding antithyroid drug administration will block I^{131} uptake.[12] This effect may wear off in one to four days but may require several months before uptake again becomes sufficient to permit treatment with the isotope.

The incidence of malignant thyrotrophic exophthalmos after I^{131} therapy deserves mention. This complication has been seen at the Presbyterian Hospital following chronic treatment with antithyroid drugs and is well known after surgery. It is apparently not a particular hazard of external radiation therapy although eye changes have been noted after the use of I^{131}, both in the present series and elsewhere.[34] These changes have been relatively mild in the present experience and became arrested before much advance occurred. This halt in progression was associated with the administration of thyroid but may have been spontaneous. Since all modalities of treatment for toxic goiter entail the risk of subsequent malignant exophthalmos, except possibly x-radiation, there is no particular choice between the other methods and I^{131} in this respect, at least according to present information. However, definitive therapy for the hyperthyroid aspect of the syndrome probably should be avoided where malignant exophthalmos appears a likely aftermath, unless relief of toxicity becomes absolutely necessary. If I^{131} then should be employed, smaller dosage than usual is probably advisable. This may avoid too sharp and rapid a reduction of circulating thyroid hormone, with consequent release of excess thyrotrophin by the anterior pituitary, a possible cause for worsening of malignant exophthalmos according to the pituitary concept of pathogenesis.[35]

The treatment of toxic nodular goiter with I^{131} has been avoided in the present series, with one or two exceptions. The incidence of complicating malignancy in a nodular goiter with hyperthyroidism is extremely low. Nevertheless, a nodule represents a complication of hyperthyroidism and therefore surgery would seem to be the treatment of choice. Crile has found this type of goiter to be unusually resistant to I^{131}, requiring unusually high dosages of the isotope to establish remission.[24]

Finally, the transient flare-up in toxicity which may follow I^{131} therapy deserves note. This is a real increase in hyperthyroidism and is associated with a rise in serum precipitable iodine titer.[19] As a consequence, there exist the possibilities of cardiac failure and of the onset of arrhythmia. These should be watched for. Also there is a definite awareness by the patient of the exaggerated toxicity and increasing anxiety becomes apparent. Warning of the possibility of this event may help a little in tiding the patient

over this period. Studies are now in progress to establish whether stable iodine or antithyroid drug administered subsequent to I^{131} therapy may not avoid this complication without at the same time interfering with the efficacy of the isotope.

SUMMARY

1. The results of I^{131} therapy for toxic goiter are presented. One hundred three patients were treated with dosage between 3 to 6.5 mc.

2. The method used and the calculation of radiation are outlined.

3. The results are analyzed in terms of number of treatments, total dosage per treatment, dosage per estimated Gm. of thyroid tissue and radiation received by the gland. About 92 per cent of all the patients were relieved of hyperthyroidism; about 97 per cent in those treated more recently.

4. The use of radioiodine therapy in primary previously unoperated goiter should be restricted in general to the older age groups.

5. I^{131} is the method of choice in treating recurrent toxic goiter, when hyperthyroidism has reappeared after surgery.

6. The important complications affecting I^{131} therapy are discussed.

REFERENCES

1. Hertz, S. and Roberts, A. Radioactive iodine in the study of thyroid physiology: use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.*, 81: 131, 1946.
2. Hamilton, J. G., Soley, M. H. and Eichhorn, M. B. Deposition of radioactive iodine in human thyroid tissue. *Univ. California Publ. Pharmacol.*, 1: 339, 1940.
3. Werner, S. C., Quimby, E. H. and Schmidt, C. Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine; eight day half life. *Radiology*, 51: 564, 1948.
4. Werner, S. C., Quimby, E. H. and Schmidt, C. The clinical use of radioactive iodine. *Bull. New York Acad. Med.*, 24: 549, 1948.
5. Werner, S. C., Quimby, E. H. and Schmidt, C. Brookhaven Conference Report on Radioiodine, Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
6. Chapman, E. M. and Evans, A. D. The treatment of hyperthyroidism with radioactive iodine. *J. A. M. A.*, 131: 81, 1946.
7. Seidlin, S. M., Marinelli, L. D. and Oshry, E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. *J. A. M. A.*, 132: 838, 1946.
8. Chapman, E. M., Skanse, B. N. and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. *Radiology*, 51: 558, 1948.
9. Quimby, E. H. Brookhaven Conference Report on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
10. Feitelberg, S. Brookhaven Conference report on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
11. Stanley, M. M. and Astwood, E. B. The accumulation of radioactive iodine by the thyroid gland in normal and thyrotoxic subjects and the effect of thiocyanate on its discharge. *Endocrinology*, 42: 107, 1948.
12. Werner, S. C., Quimby, E. H. and Schmidt, C. J. The use of tracer doses of radioactive iodine, I^{131}, in the study of normal and disordered thyroid function in man. *J. Clin. Endocrinol.*, 9: 342, 1949.
13. Oshry, E. and Schmidt, C. Brookhaven Conference Report on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
14. Unpublished data.
15. Soley, M. H., Miller, E. R. and Foreman, N. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
16. Marinelli, L. D., Quimby, E. H. and Hine, G. J. Dosage determination with radioisotopes; practical considerations in therapy and protection. *Am. J. Roentgenol.*, 59: 260, 1948.
17. Barker, S. B. Determination of protein bound iodine. *J. Biol. Chem.*, 173: 715, 1948.
18. Hamilton, H. and Werner, S. C. Unpublished data.
19. Riggs, D. S. Elevation of serum protein bound iodine after large doses of radio-active iodine. Federation Proc., 7: 251, 1948.
20. Chapman, E. M. Brookhaven Conference Reports on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
21. Miller, E. R., Soley, M. H. and Dailey, M. E. Preliminary report on the clinical use of radioactive iodine I^{131}. *Am. J. Roentgenol.*, 60: 45, 1948.
22. Prinzmetal, M., Agress, C. M., Bergman, H. C. and Simkin, B. Toxic goiter. *J. A. M. A.*, 140: 1082, 1949.
23. Crile, G., McCullagh, E. P. and Glasser, O. Experience with radioactive iodine in the treatment of hyperthyroidism. *Cleveland Clin. Quart.*, 16: 1, 1949.
24. Haines, S. F., Keating, F. R., Power, M. H., Williams, M. D. and Kelsey, M. P. The use of radioiodine in the treatment of exophthalmic goiter. *J. Clin. Endocrinol.*, 8: 813, 1948.
25. LeBlond, C. P., Tertman, M. B., Puppel, I. D. and Curtis, G. M. Radioiodine autography in studies of human goitrous thyroid glands. *Arch. Path.*, 41: 510, 1946.
26. Quimby, E. H. and Werner, S. C. Late radiation effects in roentgen therapy for hyperthyroidism. *J. A. M. A.*, 140: 1046, 1949.
27. Chapman, E. M. Personal communication.
28. Sloan, L. W. Unpublished Data.
29. Bjorneboe, M. Re-examination of 79 x-ray treated patients 8–18 years after their discharge. *Acta med. Scandinav.*, 117: 15, 1944.

30. MENVILLE, L. J. Radiologic aspect of thyrotoxicosis. *Radiology*, 18: 568, 1932.
31. WILLIAMS, R. H., ASPER, S. P. and ROGERS, W. F. Persistence of remissions of thyrotoxicosis after cessation of Thiouracil Therapy. *New England J. Med.*, 236: 737, 1947.
32. ARANOW, H., ELLIOTT, R. H. E., FRANTZ, V. K., MEICHER, G. W. and WERNER, S. C. Thiouracil in the treatment of thyrotoxicosis. *Ann. Surg.*, 124: 167, 1946.
33. CHAPMAN, E. M. Personal communication.
34. CHAMBERLAIN, R. Discussion. Am. Radium Soc., June, 1949.
35. SMELSER, G. A comparative study of experimental and clinical exophthalmos. *Am. J. Ophth.*, 20: 1189, 1937.

Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis*

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THIS report deals with observations on eight patients with rheumatoid arthritis who have been treated with adrenocorticotrophic hormone (ACTH). The dramatic symptomatic response of patients with rheumatoid arthritis to the administration of ACTH described by Hench et al.[1] has been amply confirmed.

An understanding of the mechanism of this response or, in fact, of the mechanism of the activity of rheumatoid arthritis has not yet been found. Before the advent of cortisone and ACTH for clinical usage any decrease in activity of rheumatoid arthritis, when it occurred, took place gradually. With ACTH, and as reported by Hench with cortisone,[1] a rapid and complete defervescence of activity takes place and activity usually returns when the medication is discontinued. This type of response suggests that the primary cause of the disease may not be affected by the administration of cortisone or ACTH, the effects being only on those factors which constitute the reaction of the host to the mechanisms that initiate and sustain the disease. These secondary factors constitute what is vaguely termed "activity" of the disease. Some of them are purely subjective, such as pain, easy fatiguability, lassitude and general malaise. Others are objective and capable of measurement, such as the inflammation of the joints, rapid erythrocyte sedimentation rate, fever and anemia.

Most of our studies to determine the mode of action of ACTH in rheumatoid arthritis gave negative results. The data are recorded to save repetition on the part of subsequent workers on this problem. A few possible leads as to the mechanism of action are presented but these require more extensive study and confirmation.

CLINICAL DATA

Plan of Treatment. Eight patients with rheumatoid arthritis have been treated with ACTH. All received the hormone intramuscularly in divided doses every six hours, save for one woman, aged sixty-two, who was treated for seventeen weeks. At the start this woman received 60 mg. a day. An attempt was made to discover the lowest dose capable of inducing remission. With 5.0 mg. three times a day, pain and stiffness recurred. With 10 mg. twice a day she was relatively free of activity. She was maintained on 20 mg. a day in two doses for six weeks, then treatment was stopped for thirty-six hours when symptoms of muscle aches, stiffness and joint pains recurred; treatment with 25 mg. a day in two doses was then resumed. One man, aged thirty-nine, received ACTH for twenty-seven days. He remained in remission on the initial dose of 60 mg. a day for six days. This was reduced to 40 mg. a day for eleven days, and then to 30 mg. a day for seven days. On dosages of 15 mg. a day for three days symptoms recurred in a mild form. The remainder of the patients were three men aged forty-three, forty-five and forty-nine, and three women, eighteen, thirty-four and forty. These patients received six to ten days of treatment with 40 mg. of ACTH daily, with an initial daily dose of 100 mg. Two of these patients received a second course of six and

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seven days following a twenty-one-day interval without the hormone. The age of the patient, the duration of disease in each and the duration of ACTH treatment are shown in Table 1.

Subjective Response. The dramatic clinical response of the patient with rheumatoid arthritis to the administration of ACTH has been confirmed with no exceptions. The improvement is rapid, as Hench[1] has stated, with relief of stiffness within twelve to twenty-four hours followed rapidly by a decrease in pain. The sedimentation rate fell markedly in all of our patients. We have been impressed with the rapid improvement in all clinical aspects of the disorder, joint inflammation and swelling, muscular stiffness and protective spasm, fever and tachycardia, but the most rapid change has been in the skeletal muscle component. In all patients studied the relief of stiffness after inactivity—notably on arising in the morning—has been noteworthy.

TABLE 1

CLINICAL CHARACTERISTICS AND PLAN OF TREATMENT OF EIGHT PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH ACTH

Patient	Sex	Age	Duration of Rheumatoid Arthritis (yr.)	Other Complicating Diseases	Duration of ACTH Treatment	Average Daily Dose (mg.)
W. O'T.	M	45	12	Amyloid Hay fever	2 courses of 6 days	40
P. F.	F	18	4	None	2 courses of 7 days	40
M. G.	F	40	18	None	13 days	40
A. A.	M	39	1	None	27 days	40
M. M.	F	62	14	None	17 weeks	20–25
E. E.	F	34	17	None	6 days	40
N. M.	M	43	2½	None	7 days	40
G. McS.	M	49	11	Ureteral calculus Bronchiectasis	7 days	40

In all but one patient, a return of activity occurred promptly when the medication was discontinued. The exception was in a woman whose euphoria developed into a mania which persisted for eleven days after ACTH was discontinued and was terminated by electroshock therapy. Twenty-five days after ACTH was discontinued, joint pain was minimal although the erythrocyte sedimentation rate had risen slightly. The relapse in the other cases was brisk and violent and appeared within twelve to twenty-four hours of discontinuance of the drug. For a period of four to ten days following cessation the arthritis was as severe as or worse than pretreatment. However, following this violent relapse there was a period of return of well being during which some of the improvement gained during treatment was maintained.

Subcutaneous Rheumatoid Nodules. We have treated two patients who presented the typical subcutaneous nodules frequently seen in patients with rheumatoid arthritis. The nodules were juxta-articular below the olecranon process. One patient, M. M., had had a nodule removed in October, 1948, from the left forearm. This had the microscopic appearance of a typical rheumatoid nodule.[2] On the right elbow a similar nodule was present which, when treatment with ACTH was started on May 24th, was approximately the same size as that removed in October from the left. After two weeks of treatment the nodule on the right was felt to be smaller and apparently was fragmenting, as several smaller nodules could be felt. These continued to decrease in size and on June 29th, after thirty-five days of ACTH treatment during which the patient continued in remission, the nodule was removed with the olecranon bursa. The synovial surface of the bursa contained several projections which the surgeon thought were villi but on section these proved to be rheumatoid nodules with large central areas of fibrinoid necrosis surrounded by dense collagen in which were palisaded rows of large mononuclear elongated cells, similar histologically to the nodule removed before treatment with ACTH. In the area of collagen many thick-walled capillaries were seen and many fibroblasts and epithelial cells. Only occasional lymphocytes could be identified and these were less in number than in the first nodule removed before treatment. One other patient presented juxta-articular nodules on both elbows which grew much smaller on ten days' treatment with ACTH.

Flexion Contractures. It has been held that the flexion contractures which occur in a large number of patients with rheumatoid arthritis result from two factors: (1) intrinsic disease of the skeletal musculature and (2) a process secondary to muscle splinting of painful joints.[3] The more powerful flexor groups overcome the weaker extensors. In our experience, using slow-acting curare preparations, flexion contractures of recent origin may be overcome by depressing the myoneural junction.[4] With ACTH a similar but much more dramatic and less evanescent effect on flexion contractures was observed. Those of recent origin promptly returned to full extension. Those of longer duration (some five years) showed evidence of increasing extension. In these we have not continued treatment long enough as yet to state whether or not full extension may be regained but the results are definitely encouraging. Improvement was most marked in the flexion contractures, which apparently do not return as rapidly as does the symptomatic relapse or the laboratory relapse.

Heart Size. Two of the eight patients have shown a definite increase in heart size while on treatment with ACTH. No significant increase could be detected in the other six. In one patient this increase was approximately 2 cm. and was not modified by sodium restriction. The second patient showed an increase of 1.9 cm. in a six-day period of treatment with a weight gain of 3.4 Kg. On a subsequent course of ACTH for six days with fairly rigid sodium restriction there was no weight gain, an increase in heart size of only 0.5 cm. occurred and there was no decrease in hematocrit. In the other patients sodium was not restricted and slight hemodilution, as measured by hematocrit, was noted in five of six patients studied.

CHEMICAL CHANGES

Sodium and Potassium. Changes in sodium and potassium excretion have been described following the administration of ACTH.[5,6] Balance studies were made in one of our patients, A. A. This patient was maintained on a constant diet and twenty-four-hour urine sodium and potassium determinations were made, using the flame photometer.* With 60 mg. of ACTH daily there was marked retention of sodium and a minimal increase in potassium excretion. This was not mirrored in the serum sodium or potassium which changed relatively little but was associated with a weight gain of 3 Kg. When the ACTH was cut to 40 mg. per day, after six days at a dosage of 60 mg., there was a slight sodium diuresis and the gain in weight continued at a slower pace. However, the arthritis continued in remission. After eleven days at a dosage of 40 mg. the dose was decreased to 30 mg. and there was a considerable sodium diuresis with a loss of 2.2 Kg. in weight, which reached the pretreatment level. The arthritis continued in remission. After seven days at a dosage of 30 mg. the dose was reduced to 15 mg. and there was a marked sodium diuresis with weight loss to 1 kilogram below pretreatment levels. The arthritis was in partial but not complete remission although the erythrocyte sedimentation rate (ESR) remained low. After three days on a dosage of 15 mg. the drug was discontinued and in the next twenty-four hours there was a one-day diuresis of sodium followed by no further weight loss but with a very prompt return of symptoms, rise in ESR and fever.

All eight patients with rheumatoid arthritis whom we have treated have gained weight temporarily on ACTH. This weight gain has been between 1 and 4 Kg.

One patient developed a low serum potassium, 2.7 m.Eq./L. (pretreatment 4.4), after thirteen days on ACTH. Subsequently, after sixty days' treatment at a dosage of 25 mg. the serum potassium remained at about 3.7 to 3.9 m.Eq./L. while ingesting 1.8 Gm. of potassium chloride in addition to her diet. There were no symptoms associated with the low potassium level. The serum sodium concentration varied con-

* We are indebted to Dr. Kermit Pines for these determinations.

siderably and did not mirror weight changes or hemodilution.

Uric Acid Excretion. An increased excretion of uric acid has been described following the administration of ACTH.[5-9] We have followed urinary uric acid in two patients. (Figs. 1 and 2.) In one, fever in the control period may have masked any significant rise during the period of treatment. After treatment was discontinued there was a slight fall. In the other patient there was apparently a definite but small rise in uric acid excretion which decreased when medication was stopped temporarily and then rose again when ACTH was resumed.

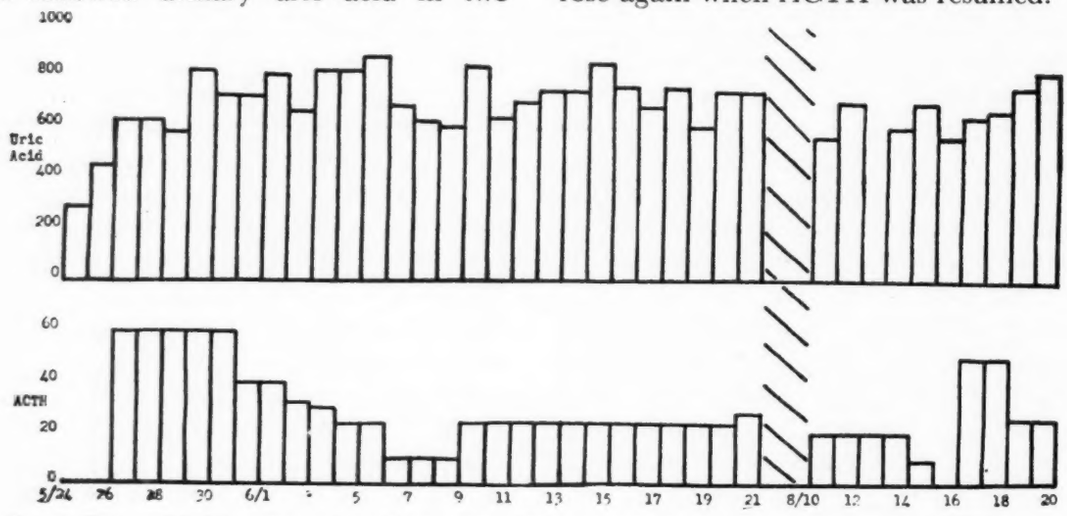

FIG. 1. Patient M. M., urine uric acid excretion. Uric acid—mg. per twenty-four hours; ACTH—mg. per twenty-four hours.

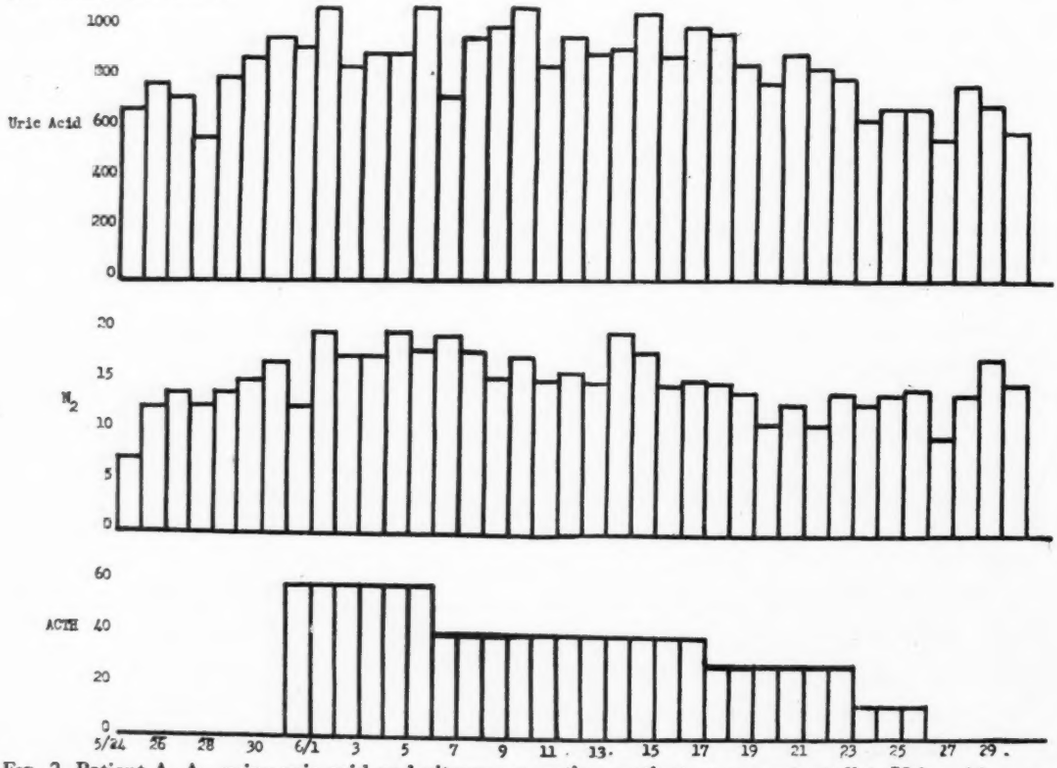

FIG. 2. Patient A. A., urine uric acid and nitrogen excretion; patient on a constant diet. Uric acid—mg. per twenty-four hours; nitrogen—gm. per twenty-four hours; ACTH—mg. per twenty-four hours.

Urine Nitrogen Excretion. An increase in urine nitrogen excretion has been described following the administration of ACTH.[5,6]

This was followed in one patient on a constant diet (Fig. 2). There was a small increase in nitrogen excretion during the initial phase but this fell to control levels when the dose was decreased although clinical and laboratory remission continued.

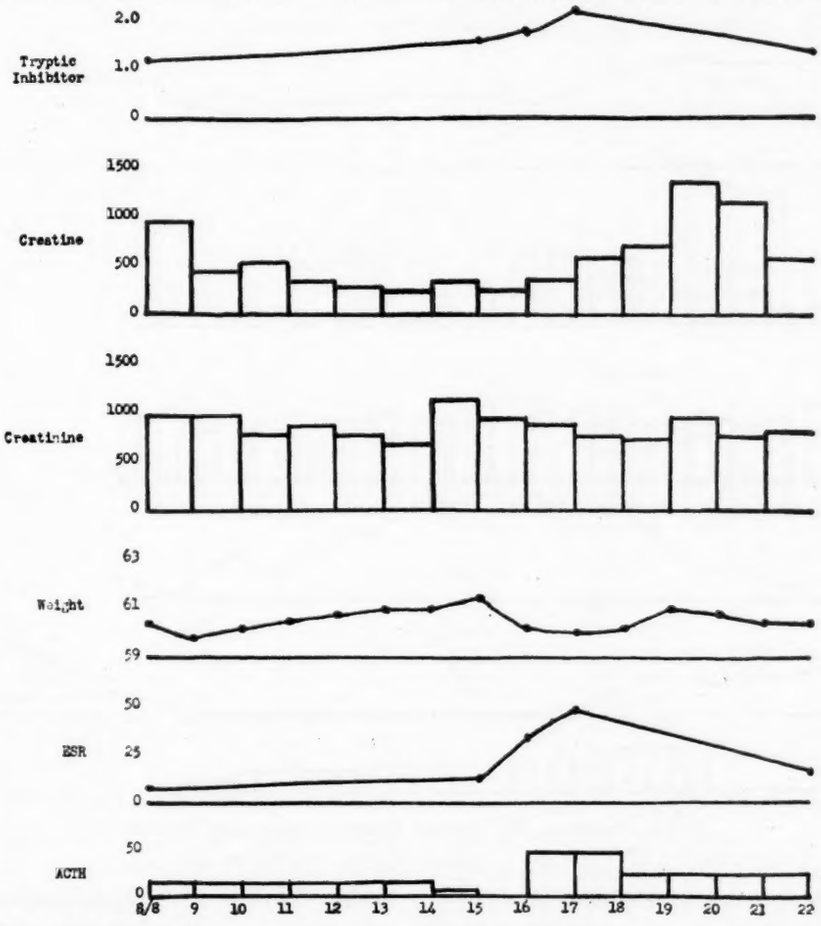

FIG. 3. Patient M. M., creatine excretion. Creatine and creatinine—mg. per twenty-four hours; weight—kg.; ESR—mm. per hour (Westergren); ACTH—mg. per twenty-four hours; tryptic inhibitor—see Table II.

Creatinuria. An increase in creatinuria following the administration of ACTH to a normal subject has been described.[6] In two patients studied there was a large outpouring of creatine (Figs. 3 and 4) at one time during the treatment period. This increased creatinuria did not continue, however, throughout the period of treatment with its attendant remission.

Serum Inorganic Phosphorus. This was followed in all patients. At some time during treatment with ACTH there was a definite drop in serum inorganic phosphorus in six of the eight patients. (Table II.) This returned to approximately pretreatment levels in two patients studied within three weeks.

Serum Proteins. The protein changes described by Hench[1] have been confirmed. There is a rapid fall in ESR in all patients. In one patient with concurrent amyloidosis this did not reach normal levels after treatment for a week. (Table II.) In another patient treated for six days the fall was not to normal. In all others normal levels were reached within a week. In all who have now been followed after treatment was discontinued the ESR returned promptly to levels at or above pretreatment levels. This rise occurred promptly, with some rise becoming manifest usually within forty-eight hours after medication was discontinued. In three patients followed after ten to thirty days' treatment there was a fall in total serum globulin and in euglobulin. Changes

in serum albumin were less consistent. The cephalin-flocculation test was positive in one patient and this became negative with treatment. (Table II.)

Tryptic inhibitor levels of the serum were followed using the method of Britten and Clark.[10] These were above the normal range in the control period in all and fell appreciably in all during treatment, to return promptly when treatment was discontinued to levels at or above those seen in the control period (Table II.) The significance of this reaction is not known.

Immunologic Changes. Approximately 50 per cent of patients with rheumatoid arthritis have in their serum an agglutinin for group A hemolytic streptococci[11] and about 60 to 70 per cent have an agglutinin for sensitized sheep cells.[12] These two antibodies were followed in all patients. There was some variability in the titer of the group A streptococcus agglutination but the reaction remained positive in all but one instance in which a positive agglutination changed to doubtful, in the patient, M. G., who developed acute mania. (Table III.) The sensitized sheep cell agglutination has shown a similar variability in titer with some diminution on treatment and a return to higher titers on discontinuation of treatment. (Table III.) Again, only one of eight patients showed a fall from the rheumatoid range to the normal range. This patient, M. G., had only a weakly positive titer in the control period and the fall was only of one tube. On subsequent examination, while still on ACTH, the titer was at the pretreatment level. Since treatment was maintained in one patient for ten weeks and in another for four weeks, and since other changes in serum proteins reverted toward normal and these agglutinins persisted, it is possible that these antibodies may represent an integral part of the disease and may not be secondary reactions to a chronic granulomatous process. It is also possible that for reasons unknown the reversion to normal of these serologic reac-

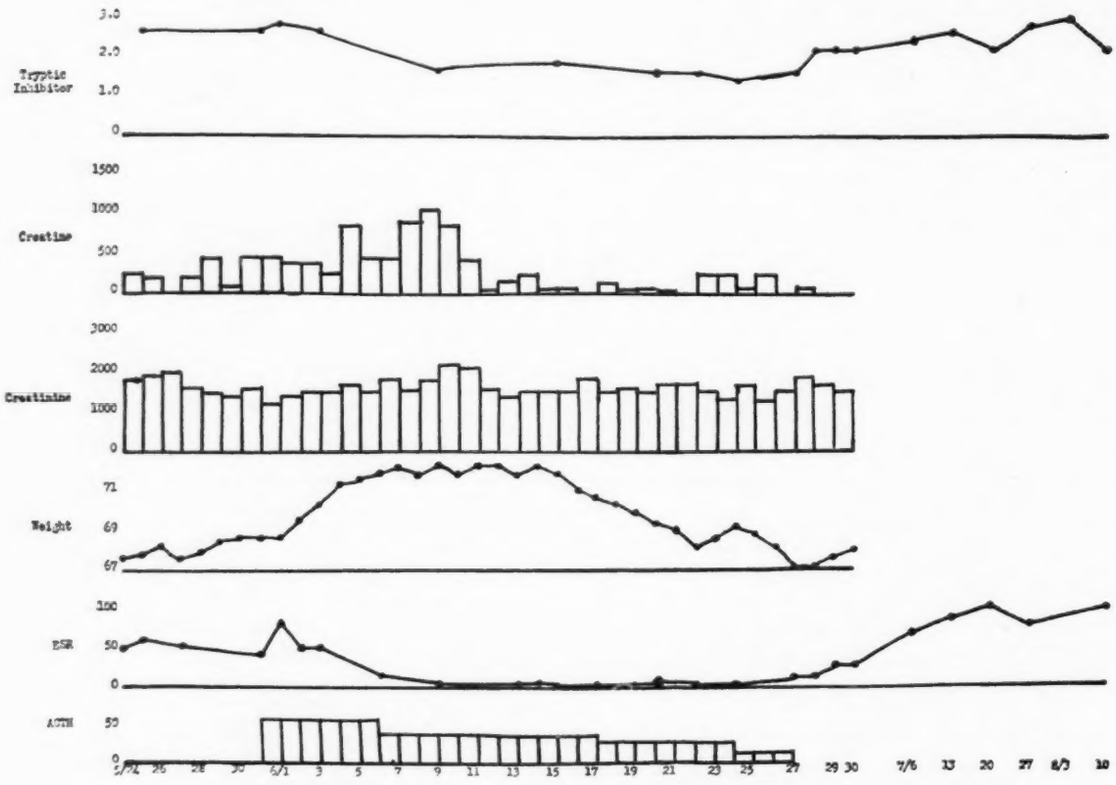

FIG. 4. Patient A. A., creatine excretion; same as Figure 3.

tions may be delayed and not take place during the period of treatment we have employed.

One patient also had an elevated anti-streptolysin-O titer. This failed to change significantly during twenty-seven days of treatment.

TABLE II
HEMATOCRIT, PROTEIN AND PHOSPHORUS CHANGES

Patient	*	Hematocrit—Per Cent Cells	Weight—Kg.	Proteins			ESR—mm. per hour Westergren	Cephalin Flocculation	Tryptic Inhibitor—mg. Equiv.†	Inorganic Phosphorus—mg. Per Cent
				Albumin—Gm. Per Cent	Globulin—Gm. Per Cent	Euglobulin—Gm. Per Cent				
W. O'T.	1	31.3	60.6	3.9	5.0	1.6	145	0	2.2	3.5
	2	27.5	63.9	3.6	3.9	0.8	90	0	1.8	3.0
P. F.	1	45.3	59.0	...	...	...	44	..	1.6	4.9
	2	40.8	61.0	...	...	...	20	..	1.2	3.4
M. G.	1	35.0	46.5	...	...	...	67	..	1.6	5.2
	2	38.0	47.6	...	...	...	5	..	1.2	2.2
A. A.	1	....	68.0	4.4	2.3	0.5	57	..	2.6	5.3
	2	....	72.3	4.4	1.7	0.	4	..	1.4	3.3
M. M.	1	....	58.1	3.6	2.1	0.	31	++	2.0	3.6
	2	....	61.4	4.1	1.7	0.	3	0	1.2	2.4
E. E.	1	31.6	42.3	...	...	...	96	++	...	3.2
	2	30.5	43.8	...	...	...	50	+	...	3.4
N. M.	1	42.1	69.4	...	...	...	76	..	...	3.8
	2	40.7	72.7	...	...	...	20	..	...	4.1
G. McS.	1	40.1	59.4	...	...	...	45	0	...	3.8
	2	36.4	60.3	...	...	...	14	..	...	2.8

* 1, Control; 2, during treatment.
† mg. equivalent to crystalline soya bean inhibitor when equal amounts of crystalline soya bean inhibitor and crystalline trypsin neutralize.

Cholesterol Partitions. These were carried out in seven patients. There is apparently a wide variation in the serum cholesterol of patients with rheumatoid arthritis treated with ACTH. In five of the patients the period on ACTH was relatively uneventful and in four of these there was a rise in cholesterol, both free and esterified. (Table IV.) There was no change in the fifth patient. One patient whose euphoria ended in a hypomanic or manic state showed a marked drop in total cholesterol with the percentage of esterified cholesterol falling 3 per cent. One patient had an attack of ureteral colic due to stone during the treatment period which inconvenienced him for a period of two days and this patient showed a drop in total cholesterol, again with the percentage of esterified cholesterol falling 4 per cent. The significance of these changes is not clear.

Glucose Metabolism. Changes in carbohydrate metabolism following the administration of ACTH have been observed.[5,7] Frequent fasting blood-sugar determinations were made during the treatment period in two patients who received ACTH for relatively long periods. Both of these patients given 60 mg. of ACTH daily showed a slight elevation in fasting blood sugar, from 85 to 120 mg. per cent. However, when the dose was lowered to 40 mg. a day, while the remission of the arthritis persisted the fasting blood-sugar levels approached those seen in the control period. Neither of these patients showed a significant glycosuria. In none of the other patients did a definite glycosuria appear. No sugar tolerance studies were carried out.

TABLE III
IMMUNOLOGIC CHANGES

Patient	*	Streptococcus Agglutination			Sensitized Sheep Cell Agglutination
		Result	Highest Titer	First Tube	
W. O'T.	1	negative	0	0	16
	2	negative	0	0	32
P. F.	1	positive	1/640	++	64
	2	positive	1/640	++	32
M. G.	1	positive	1/640	++	16
	2	doubtful	1/160	+±	32
A. A.	1	positive	1/320	++	512
	2	positive	1/160	++	32
M. M.	1	positive	1/320	++	512
	2	positive	1/320	++	64
E. E.	1	positive	1/320	++	256
	2	positive	1/320	++	1024
N. M.	1	positive	1/640	++	32
	2	positive	1/640	++	16
G. McS.	1	doubtful	1/80	+±	128
	2	doubtful	1/80	+±	64

* 1, Control; 2, during treatment.

Excretion of Glucuronic Acid and Gentisic Acid. With salicylate ingestion there is a prompt rise in urine glucuronic acid[13] and in an ether-soluble chromogen believed to be gentisic acid.[14] Two patients receiving ACTH were followed for glucuronic acid and gentisic acid excretion. There was no increase in either. Thus two of the chemical

accompaniments of salicylate ingestion were not seen following the administration of ACTH.

Mental Changes. In all these patients there was some degree of the "euphoria" described by Hench.[1] It is to be noted that in two of our patients on the second course of treatment with a similarly dramatic remission there was less of this euphoria. However, a constant finding has been a subjective sense of mental alertness, most marked at night. The patients state that they keep thinking and are unable to sleep. One patient was subjected to psychometric tests during treatment and after it was discontinued. No appreciable difference could be elicited. Electroencephalograms have been done in all.* During treatment there appears, at variable times, an abnormal EEG pattern manifested by the appearance of increasing amounts of slow (5/second) activity. This appeared in six of the eight patients and disappeared when the medication was discontinued.

TABLE IV
CHOLESTEROL PARTITIONS

Patient	*	Cholesterol—Mg. Per Cent			Ester—Per Cent
		Total	Free	Ester	
W. O'T.	1	173	52	121	70
	2	204	66	138	68
P. F.	1	158	45	113	72
	2	178	49	129	73
M. G.	1	171	46	125	73
	2	138	42	96	70
M. M.	1	195	47	148	76
	2	206	57	149	72
E. E.	1	178	49	129	74
	2	172	46	126	73
N. M.	1	204	58	146	72
	2	229	66	163	71
G. McS.	1	260	76	184	71
	2	199	65	134	67

* 1, Control; 2, during treatment.

Evidences of Hyperadrenalism. Hench[1] has described the moon facies, striae, amenorrhea, hirsutism and acne appearing in patients treated with cortisone and ACTH. In almost every one of our patients, upon careful search, some evidence of hyperadrenalism could be detected associated with remission of the arthritis. This was manifested either as moon facies, slightly increased uric acid excretion, slight changes in carbohydrate metabolism, retention of sodium or a lowered serum potassium concentration.

COMMENTS

These patients with rheumatoid arthritis were maintained in a state of remission on ACTH.* The arthritis was completely quiescent and only irreversible changes in bones and joints remained in the relatively short periods of treatment employed. With the dosage schedule used for control of rheumatoid arthritis there was minimal sodium retention, most readily detected by a sodium diuresis following withdrawal. Increase in nitrogen and uric acid excretion was minimal. Serum inorganic phosphorus may be temporarily decreased in some of the patients. A temporary but striking creatinuria appeared with treatment. The variability in serum cholesterol follows no pattern and needs more elucidation.

Reversion of the various protein abnormalities to normal under ACTH treatment and their return to pretreatment levels upon cessation of treatment suggests that these are associated with "activity" of the disease resulting from the host response. Included in this group of disturbances are serum globulin, cephalin flocculation, ESR and tryptic inhibitor levels. Serologic findings characteristic of rheumatoid arthritis remained abnormal in all but one instance, at least for the duration of therapy we have used. The pathogenesis of these serologic changes is unknown but apparently these alone of the many clinical and laboratory findings described may persist for relatively long periods of remission induced by ACTH. It is consequently possible that these changes

* We wish to thank Dr. Paul Hoefer for performing these for us. These results will be reported in detail in a subsequent paper.

* We wish to thank Dr. John R. Mote, Medical Director of The Armour Laboratories, Armour & Company, for the supply of ACTH.

are associated with the primary disease process and may not be secondary to it. Be that as it may, it seems apparent that the underlying disturbance continues to be present in a patient with rheumatoid arthritis maintained on ACTH in complete objective and subjective remission. In our experience when the hormone was discontinued, prompt resumption of symptoms and laboratory and clinical signs took place in seven of eight patients. It is possible that, when sustained remissions follow ACTH therapy, a spontaneous remission such as is encountered in the natural history of the disease has taken place.[15]

It is of interest and perhaps of importance that many patients in the course of improvement under treatment with ACTH or cortisone develop a variety of disturbances characteristic of hyperadrenalism. Thus Hench,[1] as stated above, has described the development of moon facies, striae and mild hirsutism, etc., of Cushing's syndrome. Similar changes have been observed by us. Sodium retention persisted on small amounts of ACTH. The patient maintained for seventeen weeks on ACTH developed the facies of Cushing's disease. One patient with lupus erythematosus disseminatus, who had developed moon facies, died from pulmonary infarction after three weeks of treatment with ACTH. At postmortem examination the adrenals were three times the normal size. A slight increase in uric acid excretion was found to be present during remission. It thus seems possible that in order to produce and maintain clinical remission with ACTH some measure of hyperadrenalism must be induced.

While the responses to ACTH cover a broad spectrum of metabolic changes, it is possible that the remission in rheumatoid arthritis reflects the effect of excessive amounts of adrenal steroid upon mesenchymal tissue. Three patients have been observed who apparently formed granulation tissue poorly while being treated with ACTH. The first was a patient with dermatomyositis. A muscle biopsy wound produced the day before ACTH was started required twelve days to heal while ACTH therapy was continued. A biopsy wound made the day before ACTH treatment was discontinued healed in four days. There was only a moderate elevation of fasting blood sugar (71 to 90 mg. per cent) during treatment with ACTH. One patient with lupus erythematosus disseminatus (LED) developed severe symptoms postpartum. An episiotomy wound made at the time of delivery failed to heal but profuse granulation tissue was seen in this wound at the time we first saw her twenty-five days after delivery. She developed a decubitus ulcer shortly after ACTH was started and up to the time of her death from pulmonary infarction after eighteen days on ACTH, very little granulation tissue appeared in this ulcer. It is to be noted that up to three days before death she was making excellent progress and the symptoms of LED were controlled. The third patient was also one with LED. While under treatment with ACTH she developed a suppurative parotitis and an abscess on her back. It was necessary to incise and drain both of these. While on ACTH little or no granulation tissue appeared in either wound. After twenty-eight days on ACTH she developed a full moon facies and abdominal striae; the symptoms of LED were apparently controlled. Within twenty-four hours after cessation of ACTH, symptoms of LED returned and four days after the hormone had been stopped, granulation tissue could be seen in the wounds. No significant hyperglycemia was noted during treatment with ACTH. As a corollary to these observations may be cited the well recognized weakness of supporting tissues in Cushing's syndrome.

It has been postulated[16] that rheumatoid arthritis is a disease in which the mesenchymal tissues are overactive and thus it is possible that excessive amounts of adrenal steroids may depress the activity of the mesenchymal tissues and thereby depress the host responses which cause the "activity" of the disease.

CONCLUSIONS

1. There is a striking and prompt remission of the symptoms of rheumatoid arthritis in patients treated with ACTH.

2. Following cessation of therapy in seven of eight patients there was a prompt symptomatic relapse.

3. Protein changes—serum globulin, ESR, cephalin flocculation and tryptic inhibitor levels—followed the symptomatic remission and relapse.

4. Serologic changes—agglutination of group A hemolytic streptococci and sensitized sheep cell agglutination—changed with treatment much less than protein changes and in only one instance was the change significant.

5. It seems possible that to produce a remission in rheumatoid arthritis some measure of hyperadrenalism must also be produced.

6. Evidence is presented to suggest that with hyperadrenalism there is a depression of growth of certain mesenchymal tissues, chiefly granulation tissue.

7. It is suggested but not established that the favorable response of the patient with rheumatoid arthritis to administration of ACTH is due to the production of hyperadrenalism and a consequent suppression of the activity of mesenchymal tissue.

We wish to thank the Misses E. Bidwell, G. Carleton, J. Nellenbogen, V. Pratt and K. Vislocky for technical assistance.

REFERENCES

1. Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Preliminary report. *Proc. Staff Meet., Mayo Clin.*, 24: 181, 1949.
2. Dawson, M. H. and Boots, R. H. Subcutaneous nodules in rheumatoid (chronic infectious) arthritis. *J. A. M. A.*, 95: 1894, 1930.
3. Dawson, M. H. and Ragan, C. Chronic Arthritis. Nelson's Loose-Leaf System of Medicine. Chap. II, 1949.
4. Schlesinger, E. B. and Ragan, C. "Muscle spasm" in acute low back pain and similar syndromes. *Am. J. Med.*, 1: 621, 1946.
5. Forsham, P. H., Thorn, G. W., Prunty, F. T. G. and Hills, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.*, 8: 15, 1948.
6. Mason, H. L., Power, M. H., Rynearson, E. H., Ciaramelli, L. C., Li, C. H. and Evans, H. M. Results of administration of anterior pituitary adrenocorticotropic hormone to a normal human subject. *J. Clin. Endocrinol.*, 8: 61, 1948.
7. Conn, J. W., Louis, L. H. and Johnston, M. W. Alleviation of experimental diabetes in men by administration of reduced glutathione (GSH): metabolic implication. *Science*, 109: 279, 1949.
8. Robinson, W. D., Conn, J. W., Block, W. D., Louis, L. H. and Katz, J. Role of the anterior pituitary and adrenal cortex in urate metabolism and in gout. Official Program, 7th International Congress on Rheumatic Diseases. New York, 1949.
9. Forsham, P. H., Flink, E., Emerson, K. Jr. and Thorn, G. W. Metabolic studies on Cushing's syndrome. *J. Clin. Investigation*, 28: 781, 1949.
10. Britten, R. C. and Clark, D. G. C. In press.
11. Boots, R. H., Lipman, M. O., Coss, J. A. Jr. and Ragan, C. Immunological reactions in rheumatoid arthritis. Official Program, 7th International Congress on Rheumatic Diseases. New York, 1949.
12. Rose, H. M., Ragan, C., Pearce, E. and Lipman, M. O. Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. *Proc. Soc. Exper. Biol. & Med.*, 68: 1, 1948.
13. Meyer, K. and Ragan, C. Hyaluronic acid and the rheumatic diseases. *Mod. Concepts Cardiovas. Dis.*, 17: 1948.
14. Yü, T. F. and Gutman, A. B. Interference of gentisic acid in determination of urinary uric acid after administration of salicylates. *Federation Proc.*, 8: 1949.
15. Ragan, C. The general management of rheumatoid arthritis. *J. A. M. A.*, 141: 124, 1949.
16. Ragan, C. and Meyer, K. The hyaluronic acid of synovial fluid in rheumatoid arthritis. *J. Clin. Investigation*, 28: 56, 1949.

Some Technics for Recording the Ballistocardiogram Directly from the Body*

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BALLISTOCARDIOGRAPHY, the recording of motion imparted to the body by the motion of blood and the heart during each cardiac cycle, has been developed as a research method by Starr[1,8] and others.[3-6,10] Though the method promised to give information on the volume of blood ejected by the ventricles, it has been found unreliable under abnormal conditions since the amplitude of the waves depends on velocity rather than on volume alone. However, the curves are of value in detecting cardiac disease[1,2,5,7-9] and coarctation of the aorta.[2,5,6]

All of the reported work has been done by having the subject on a table which is mounted on springs to damp its motion and recording movements optically or by an electrical detecting device and an amplifying circuit. The latter is controlled to give a centimeter deflection of the galvanometer record for a standard pressure applied to the table. The tables are bulky, fixed installations and ballistocardiography today is in the same state that electrocardiography was prior to 1920. The instrument is precise and dependable but bulky, immovable and expensive.

Since ballistocardiograms seem to be of more value as empirical clinical indices of disease than for precise physiologic measurement of function, it seemed desirable to develop methods for clinical use. This proved to be rather simple, and the accessories needed for inscribing ballistocardiograms with standard electrocardiographic instruments are inexpensive and not particularly bulky. Records can easily be made in the ward, office, operating room or the home.

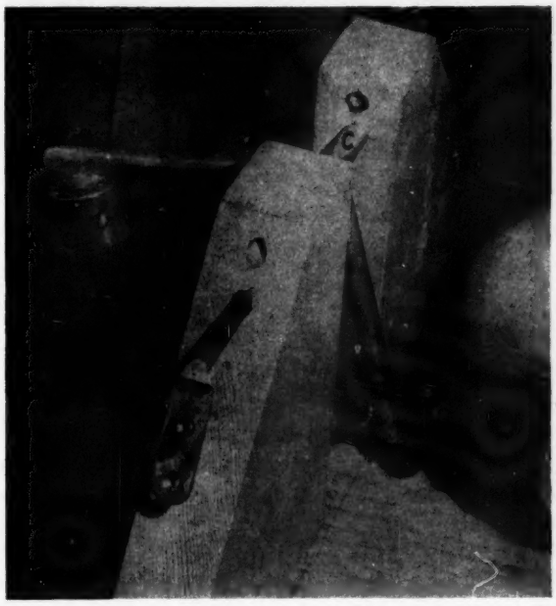

FIG. 1. Sphygmographic receiver (glycerine capsule) (*a*) mounted on head-board with counter weight (*b*). The axle (*c*) is 6 cm. wide and 1 cm. in diameter; the counterweight is 400 gm. The axle may be set either 22 or 23.5 cm. from the base board; the receiver and counterweight are centered 15 cm. from the axle.

APPARATUS AND TECHNIC

Sphygmographic Method. We learn that several others had noted that a pressure recorder, applied to the vertex of the head, gave ballistocardiographic curves; Hamilton[5] (Fig. 6) and Nickerson[3] (Fig. 4H) have published such records. We used the standard Cambridge Simplitrol pulse recording device and applied to the head either the glycerine capsule usually employed to pick up radial or femoral pulsations, or a receiver made by mounting a cork button 3 cm. in diameter on a rubber membrane 5 cm. in diameter. Either receiving device is mounted on a rigid arm 15 cm. long, extending vertically from an axle with another arm of equal length carrying a 400 Gm. counter weight at a 90 degree angle. This is mounted, as shown in Figure 1, so that the receiving capsule or

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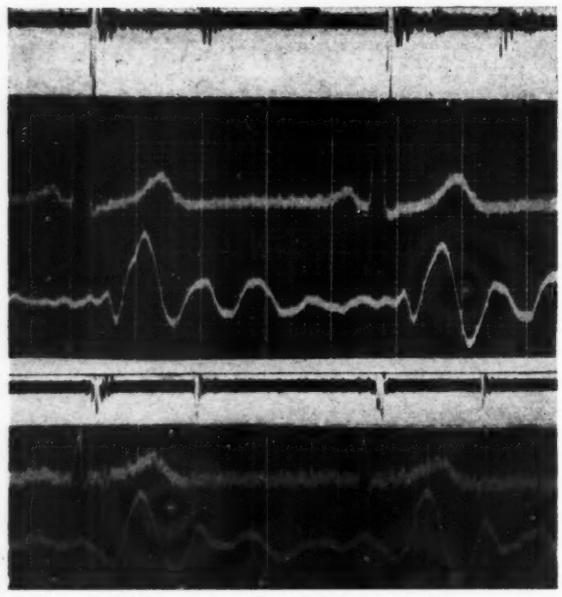

FIG. 2. Simultaneous sound, ECG and ballisto tracings made with Simplitrol.

button is held against the head with a uniform and constant pressure.

A leak in the tubing from receiving membrane to recording membrane is necessary to prevent wide respiratory swings and keep the record centered; if the leak is too large no record is inscribed. This leak is provided by a rubber tube on a Y-tube close to the recorder. It is closed with a screw clamp until release of pressure on the receiver causes a return of the shadow of the lever in 2 or 3 seconds. Another screw clamp, near this side tube but on the tube to the receiver, can be closed and gradually released until a normal subject gives oscillations of 2 cm. or more. This clamp acts as a low-pass filter and cuts out high frequency waves, either extraneous from muscle tremor, or harmonics set up in the recording system. Oscillations of frequencies below 20 per second are adequately recorded and the ballistocardiogram is faithfully reproduced. Synchronous records of heart sounds, electrocardiograms and ballistocardiograms are thus available (Fig. 2) to those who have this equipment. The time lag in the pulse recorder is 0.01 second while that in the electrical records is less than 0.001 second.

New recording capsules may be stiff and give records of low amplitude; by putting them under stretch overnight they become sensitive. The glycerine capsules or rubber membranes age and must be replaced after some months of use. Patients who are kyphotic or orthopneic do not give good records; those with coarse head tremor can not be recorded at all.

Photo-electric Method. If a piece of cardboard is firmly attached to the head and a shadow cast by its edge falls on the middle of a photocell, the electrical current recorded by the galvanometer varies with the motion of the body. When motion in the long axis of the body is recorded, the

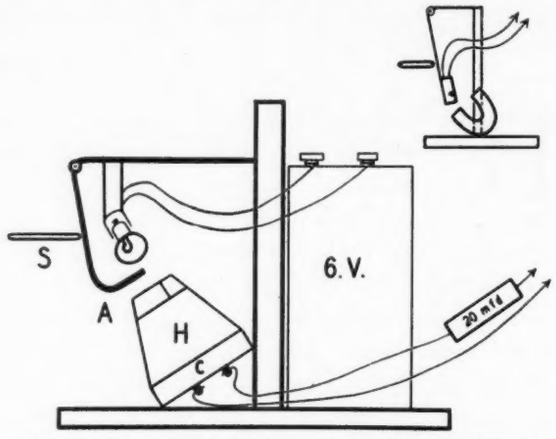

FIG. 3. Photocell ballistocardiograph with hinged occulting strip. S, strip across shins; B, hinge: C, strip casting shadow on cephalad half of the photocell, shielded by the hood. H, upper insert, Alnico magnet and coil in use as ballistocardiograph.

curves are identical with those made with the pulse recorder on the vertex. We also recorded this motion from a rigid strip of metal placed across the shins, with the legs slightly abducted and the photocell below and light source above the strip. This is possible even in orthopneic patients, and tremor of the legs is less frequent than tremor of the head. At present we use an occulting edge mounted on a hinge so that it is at a fixed distance from the bulb, and we press the hinge against the strip across the shins or against the vertex of the skull. (Fig. 3.)

We find the 890 photocell, hermetically sealed (Photovolt), gives excellent records when illuminated by a 6 volt flashlight bulb (G. E. 31). It is necessary to use a condenser (16–24 mfd) in one lead to the string galvanometer or direct writer in order to filter out or reduce respiratory movement. No amplifier is needed and there is less than 0.005 of a second time lag. The records are standard and reproducible when the galvanometer is set to give 1 cm. per millivolt deflection, and the shadow edge falls on the same part of the photocell.

The photocell and light bulb are mounted 6 cm. apart, with the cell protected from outside light by a tapered shield 3.5 cm. high. The occulting strip is 2 to 4 mm. from the bulb, and the whole apparatus is pressed toward the strip across the shins until the shadow falls on a line

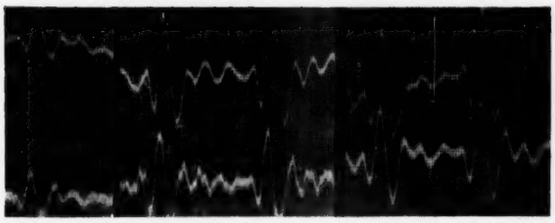

FIG. 4. Electromagnetic trace, lower, and photocell trace, simultaneous record from the shins. Note that changes in velocity (electromagnetic trace) occur 0.02 to 0.06 second before change in position becomes apparent in records A and B made without a low pass filter, while the peaks and troughs are practically synchronous in record C inscribed with the filter, in this case 100 microfarads across the leads.

marked on the light shield. Thus it falls on the same part of the cell at all times when tracings are being inscribed. The photocell terminals are connected with the arm leads of the ECG; by trial it is determined which arm lead should be attached to the condenser and which to the wire to the other pole of the cell to give an upward J wave. The terminals are then marked for right and left arm for all subsequent use.

Electromagnetic Method. When a coil of fine copper wire is substituted for the occulting strip on the hinge shown in Figure 3, and an Alnico horse-shoe magnet is mounted in place of the photocell so that the coil moves in the strongest part of the field, a galvanometer attached to the coil inscribes a ballistocardiogram when the hinge presses upon the vertex or a strip across the shins.

The relation of such curves to the photocell tracing is seen in Figure 4. The inflections precede the photocell inflections by 0.03 to 0.06 second, which is not surprizing as the velocity of body motion determines the voltage of the electromagnetic current, while displacement causes the photoelectric potential changes. The electromagnetic record picks up muscular tremor of high frequency, but this can be filtered out by putting a capacitance across the leads, and inductance in one lead on either side of the capacitance. This changes the wave phase, delaying the peaks by 0.02 to 0.06 second, so that they coincide with the photoelectric wave peaks.

This is the simplest way to record the ballistocardiograph. It may be argued that it is better to record the velocity of bodily motion than the distance moved by the body; actually the curves are so much alike that the clinical significance is unchanged. Only experience in the clinic can decide which method most effectively detects abnormalities in motion of the blood.

Effect of Mattresses and Bed Casters. Records made with patients in ward beds show varying degrees of damping and distortion, as compared with those made on a fluoroscopic table or on any rigid, smooth surface. If the bed is on casters, the records may be greatly distorted.

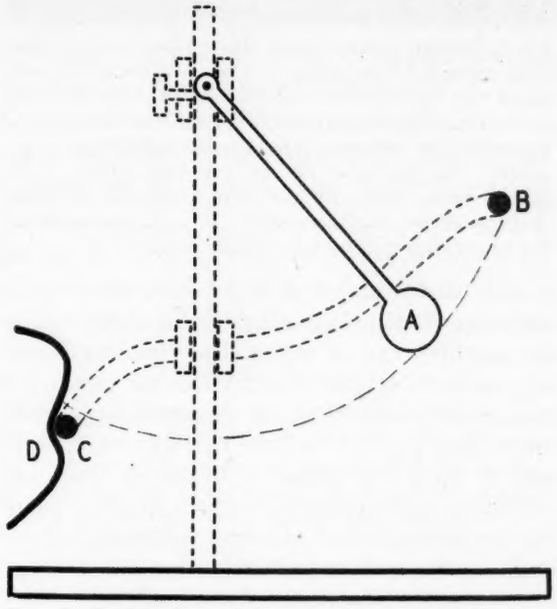

FIG. 5. Standard pendulum to deliver 200,000 dyne blow to the foot or shoulder. Arm, C, is placed against the shoulder D; pendulum A is released when in contact with upper arm B.

To get accurate records of patients in bed it is essential that the bed be rigidly held, which can be done by putting a block under the cross bars at head or foot to lift the caster off the ground about ½ inch and by putting a plywood board 18 by 32 inches under the patient's trunk and buttocks. If the mattress is of rubber foam or rests on box springs, this board must be fastened to the frame of the bed by suitable rubber-jawed clamps. Vibrations due to people walking in the building or to passing trucks may be troublesome in buildings with wooden beams and floors.

Standardization. When records are made from the head, standardization is effected by recording the effect of blows on the foot produced by a pendulum moving through a constant arc. When records are made from the legs, the blow is delivered to the right shoulder close to the neck. We use a 220 Gm. padded lead weight on an arm 12 cm. long, the length of the swing being fixed by a horizontal rod which touches the shoulder and is just beneath the arc of the pendulum and another which fixes the height to which the pendulum can be raised on the opposite side. (Fig. 5.) A 200,000 dyne blow

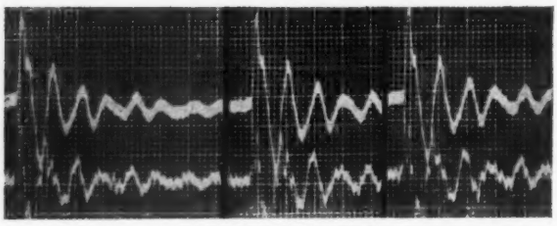

FIG. 6. Sphygmographic trace (lower) and photoelectric trace recorded from cadaver when a blow of 200,000 dynes was applied to the sole of the foot. Note progressive decrease in large oscillations, and the fine oscillations when no damping is used in the sphygmographic system. The photoelectric cell was used at the shin, but its peaks follow the sphygmographic one because of delay in the amplifier used in this original method. No amplifier is needed with the 890 cell.

gives a deflection of 8 to 10 mm. on subjects weighing 70 Kg. When using the direct writer the amplifier can be adjusted to give this deflection on each subject. In practice we rarely use this except when following change in amplitude under therapy, and with the string galvanometer merely record a series of blows so that any variations in the recording system will be evident on the records. The inherent frequency of the body is also evident from the after-waves.

COMMENT

When the foot or shoulder of a cadaver on a table is tapped, the whole body is displaced, sliding on the panniculus and returning by oscillations to the initial position. (Fig. 6.) Each after wave is 50 to 70 per cent as high as the preceding opposite wave, and the frequency depends on the weight of the cadaver, thickness of fat pads, tissue turgor and elasticity, etc. During life the recumbent body is displaced by recoil from acceleration of the viscera and blood, or from their deceleration. Displacement is resisted and after-oscillations are set up by the panniculus since every displacement stretches pannicular fibers.

Actual motion is a resultant of displacing and restoring forces, with after-waves sometimes in phase and at others out of phase with subsequent displacing forces. The actual height of the waves set in motion by systole is dependent on velocity of cardiac ejection as much as on its volume, and except for the initial (presumably auricular) H wave, the height of each subsequent wave may, by chance, be augmented or diminished by 60 per cent of the preceding wave, depending on the inherent frequency of the body. For this reason the stroke volume calculated from these waves varies from the true value in many normal subjects. At best one can conclude that large I and J waves indicate high velocity and probably large volumes of systolic ejection, small ones low velocity and probably small volumes of ejection.

If the body could be suspended in space, without friction or periodicity of the system, a true ballistic record free of restoring forces would be inscribed and the body would move away with increasing velocity. In practice the body must rest on a surface and in the past all recording has been done from the table on which it rests. Since the table is rigidly held, the body continues to move and energy is converted to heat in the panniculus. If the table has a frequency of over 10 per second, the curves inscribed are almost identical with those inscribed from the head or legs directly. Physiologically, there is no more reason for recording the motion of the body through the table than for recording cardiac action currents from a bath tub. In practice, direct recording is much more useful. As the physiologists have pointed out, the ballistocardiograph is of value chiefly for clinical purposes and the urgent problem is to determine the significance of altered patterns "in relation to disease and prognosis."[5,12]

CLINICAL SIGNIFICANCE OF ALTERED BALLISTOCARDIOGRAPHIC PATTERNS

In our own experience, patients with high cardiac output, even with heart failure, often have large I-J waves; those with low output or normal output may have very small waves, especially during expiration, if they are in failure, or even if they have angina of effort without congestive failure. Men under thirty-five who have recovered from myocardial infarction may show normal curves but many older men have bizarre tracings as the first objective sign of coronary disease. Starr noted that this may precede subjective or objective evidence of heart

disease.[9] In coarctation without failure the K wave is abruptly cut off at or above the base line.[2,5,6] After severe hemorrhage H waves are high; K waves disappear. In acute myocardial infarction low amplitude bizarre complexes repeatedly have preceded any change in the limb leads of the ECG, and in a few instances preceded the change in precordial leads.

Of particular interest to us have been the waves in diastole. Large L waves have been encountered in acute rheumatic carditis in children and adults; in normal children L waves tend to be more evident than in adults. In rheumatic carditis with mitral valve disease the L wave may be larger than J. Deep K waves occur in hypertension, with notched J waves and late K (or in reality, M) waves as failure sets in. There may be deep M waves with protodiastolic gallop, and a deep wave may precede the H wave in cases of presystolic gallop. The footward diastolic waves, in amplitude and steepness of contour, may exceed any wave due to ventricular ejection and aortic flow. Presumably they are due to deceleration of blood returning to the ventricles. The failing heart fills faster than it empties. As a rule gallop sounds occur with the deep diastolic waves but the waves may be evident before gallop is noted or persist after it has become inaudible as a result of therapy.

It seems probable that the decrease in K waves in shock is due to splanchnic and renal vasoconstriction and vasoconstriction in the skin and muscles of the legs. It may well provide anesthetists and surgeons with the first clue to the body's reaction to decreased venous return, and thus permit them to follow the onset and recovery from shock.

The ballistocardiogram gives information of a character so unlike that of the electrocardiogram and so useful to the clinician as evidence of altered circulatory conditions that it deserves wide study and application. This is now available to all who have electrocardiographic equipment, with little additional apparatus. While synchronous electrocardiograms or sound tracings are needed to identify bizarre waves, they are not needed to distinguish normal from abnormal records.

SUMMARY

1. The motion of the body recorded by a sphygmograph applied to the head, by a photocell partly shaded by a ruler across the shins, or by a coil in a magnetic field, provides a satisfactory ballistocardiogram.

2. The records require little additional equipment for those who have portable electrocardiographs. They can be made in the ward, office, operating room or at home.

3. The records are particularly useful in angina, myocardial infarction and in shock.

REFERENCES

1. Starr, I., Rawson, A. J., Schroeder, H. A. and Joseph, H. R. Studies on the estimation of cardiac output in man and of abnormalities in cardiac function from the heart's recoil and the blood's impacts; the ballistocardiogram. *Am. J. Physiol.*, 127: 1, 1939.
2. Nickerson, J. L. Some observations on the ballistocardiogram with special reference to the H-K waves. *J. Clin. Investigation*, 28: 2, 1949.
3. Nickerson, J. L. and Curtis, H. J. The design of the ballistocardiograph. *Am. J. Physiol.*, 142: 1, 1944.
4. Nickerson, J. L. The low frequency critically damped ballistocardiograph. *Federation Proc.*, 4: 201, 1945.
5. Hamilton, W. F., Dow, P. and Rennington, J. W. Relationship between cardiac ejection curves and ballistocardiographic forces. *Am. J. Physiol.*, 144: 557–570, 1945.
6. Brown, H. R., Hoffman, M. J. and De Lalla, V., Jr. Ballistocardiogram in coarctation of the aorta. *New England J. Med.*, 240: 775–778, 1949.
7. Brown, H. R., Jr. and De Lalla, V., Jr. Deep J-K stroke associated with hypertension. (Unpublished data.)
8. Starr, I. and Schroeder, H. A. Ballistocardiogram. II. Normal standards, abnormalities commonly found in diseases of the heart and circulation and their significance. *J. Clin. Investigation*, 19: 437–450, 1940.
9. Starr, I. The Ballistocardiograph—An Instrument for Clinical Research and in Routine Clinical Diagnosis. The Harvey Lectures, 194–219, 1946–47.
10. Brown, H. R., Jr. and Pearson, R. New electronic method for simultaneous recording of ballistocardiograph and electrocardiograph. *Am. Heart J.*, 35: 756–762, 1948.
11. Starr, I. Further clinical studies with the ballistocardiograph; on abnormal form, on digitalis action, in thyroid disease, and in coronary heart disease. *Tr. A. Am. Physicians*, 49: 180, 1946.
12. Tanner, J. M. The construction of normal standards for cardiac output in man. *J. Clin. Investigation*, 28, 567, 1949.

Effects of Clockwise Rotation of the Heart on the Electrocardiogram*

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IT has been pointed out by the author[1–3] and by others[4] that the position of the heart is not fixed within the thoracic cage, and that rotation of the heart can take place around one or more of the following three axes: (1) rotation of the heart around its anteroposterior axis; when this happens, the heart becomes vertical or horizontal; (2) rotation of the heart around its long axis; clockwise rotation causes the right ventricle to face more of the anterior surface of the chest wall and the left ventricle rotates to the left; counterclockwise rotation causes the left ventricle to face more of the anterior chest wall, and the right ventricle rotates to the right; (3) rotation of the apex of the heart around its transverse axis; the apex is either rotated forward or backward.

In this paper the effects of clockwise rotation of the heart in both the precordial leads and the extremity leads will be described for both normal tracings and tracings showing signs of right or left ventricular hypertrophy. The cases illustrated were selected at random from our files.

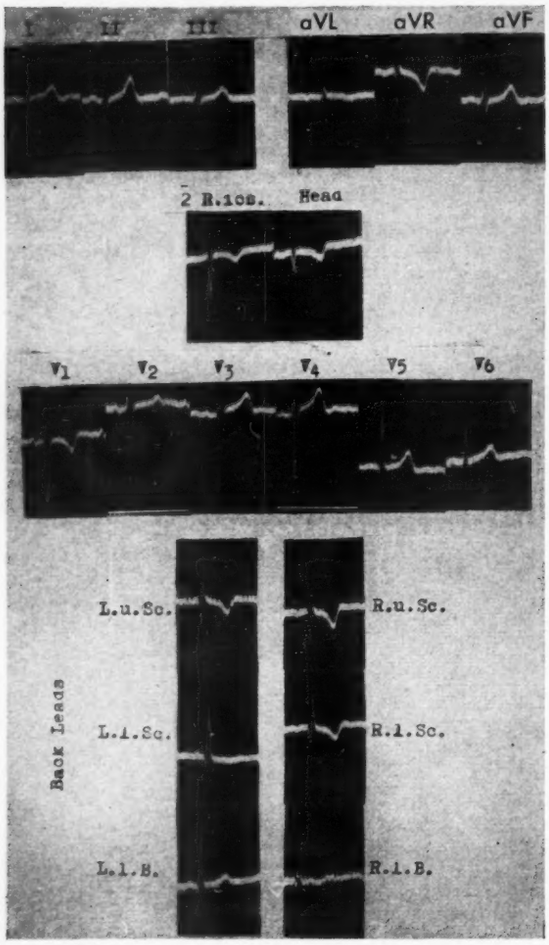

FIG. 1. Multiple unipolar leads from a normal person.

GENERAL REMARKS

In order to correlate the electrocardiographic patterns that appear in the standard leads, augmented unipolar extremity leads, and multiple precordial leads, the following review is of value:[1–3]

1. A unipolar lead that overlies or faces the epicardial surface of the left ventricle shows a qR pattern. (Fig. 1, Lead V_5.)

2. A unipolar lead that overlies or faces the epicardial surface of the right ventricle shows an rS or an RS pattern. T is usually upward but may be downward. (Fig. 1, Leads V_{1-4}.)

3. A unipolar lead that faces the right ventricular cavity shows an rS pattern and a downward T (Fig. 1, Lead $2R_{ics.}$)

4. A unipolar lead that faces the left

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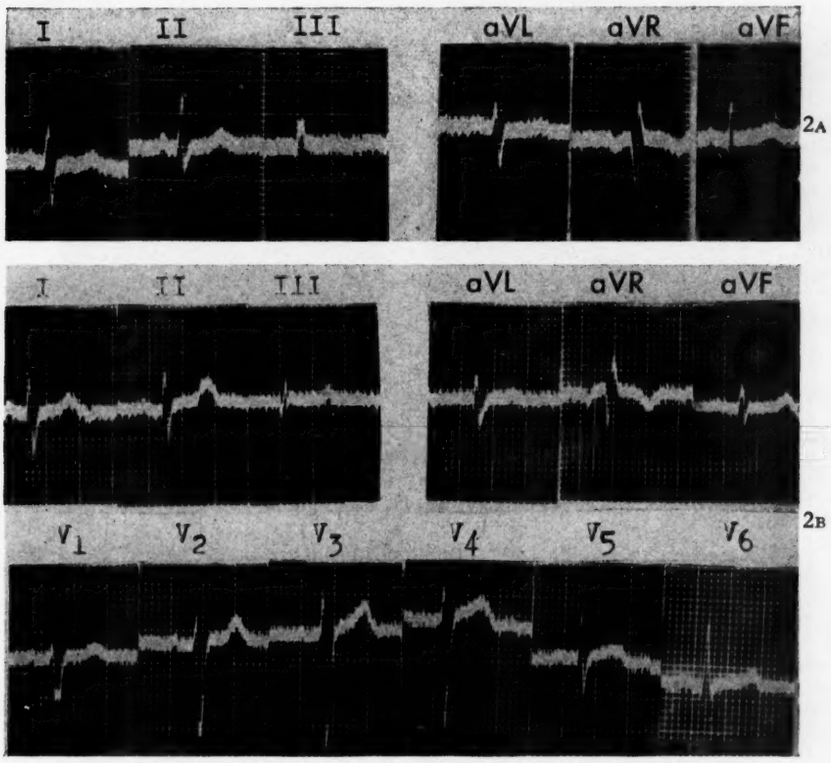

FIG. 2. The effect of marked clockwise rotation on a normal vertical heart. A is a woman, aged twenty years; B is a man, aged twenty-nine years.

ventricular cavity shows a QS deflection and a downward T. (Fig. 1, Lead Head.)

5. A unipolar lead that faces the back of the heart shows a QR (or a Qr or a qR) pattern and a downward T. (Fig. 1, Leads L.u.Sc., R.u.Sc., R.l.Sc.)

6. Although each standard lead represents a combination of potentials from two extremities, the following general relations between standard leads and unipolar extremity leads usually hold:

Lead I resembles Lead aVL or the reverse of Lead aVR.

Lead II resembles Lead aVF or the reverse of Lead aVR.

Lead III resembles Lead aVF or the reverse of Lead aVL.

7. When the heart is vertical, Lead aVL shows a QS, an rS or RS pattern. When the heart is horizontal, Lead aVL shows a qR or a QR pattern.

EFFECT OF MARKED CLOCKWISE ROTATION ON A VERTICAL HEART

When marked clockwise rotation of a vertical heart occurs, precordial Leads V_1 through V_5 or V_6 may face the epicardial surface of the right ventricle and show rS and RS patterns. (Fig. 2.) Lead aVL shows an rS or RS pattern because it faces either the cavity of the right ventricle or the epicardial surface of the right ventricle as a result of the clockwise rotation. Lead aVR shows a QR type of pattern because it faces the back of the heart as a result of the marked clockwise rotation.

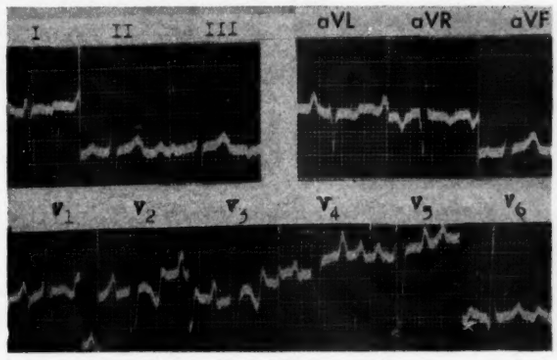

FIG. 3. The effect of clockwise rotation on a vertical hypertrophied heart.

Figures 2A and B show such tracings in normal vertical hearts with marked clockwise rotation. Figure 2B also shows an addi-

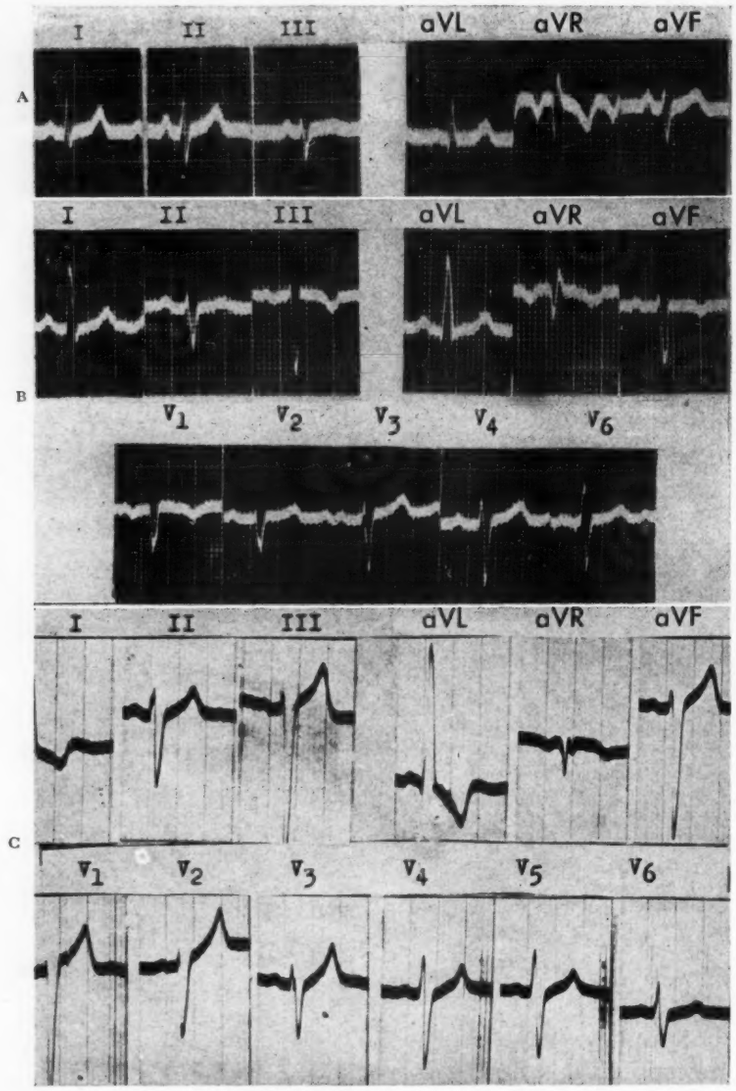

FIG. 4. A and B, the effect of clockwise rotation on normal and hypertrophied hearts with hypertensive cardiovascular disease; C, a man with hypertensive cardiovascular disease.

tional type of rotation. Ordinarily when the heart is vertical, Lead aVF faces the epicardial surface of the left ventricle and shows a qR pattern. However, if backward rotation of the apex occurs, Lead aVF faces the epicardial surface of the right ventricle and shows an rS or RS pattern as appears in Figure 2B.

Figure 3 shows the effect of marked clockwise rotation of a vertical heart in a patient who had extensive right ventricular hypertrophy. It is the tracing of a twelve year old boy who died of rheumatic heart disease. At autopsy aortic and mitral stenosis were found and there was marked hypertrophy of both the right and left ventricles.

Lead V_1 shows a tall R and a downward T due to right ventricular hypertrophy, and the P is large and wide due to auricular hypertrophy. However, Leads V_{2-5} show RS patterns which indicate that these leads are also facing the epicardial surface of the right ventricle. Therefore, marked clockwise rotation is also present. Lead aVR shows a QR and a downward T, further indicating that marked clockwise rotation is present. Lead aVL shows an rS indicating that the heart is vertical, and Lead aVF

shows an RS instead of a qR indicating that backward rotation of the apex is present.

EFFECT OF MARKED CLOCKWISE ROTATION ON A HORIZONTAL HEART

When marked clockwise rotation of a horizontal heart occurs, all six precordial leads may show rS and RS patterns just as occurs in a vertical heart so rotated, and Lead aVR develops a QR and a downward T. However, because the heart is horizontal, Lead aVL continues to show a qR pattern. Figure 4A shows this in a normal tracing. Figures 4B and C show this in patients with left ventricular hypertrophy. In Figure 4B lead aVL shows not only a qRS pattern but R is more than 13 mm. tall. This is high voltage and indicates left ventricular hypertrophy.[3] In Figure 4C Lead aVL shows not only high voltage but the depressed RS-T and downward T indicate left ventricular strain.

EFFECT OF EXTREME CLOCKWISE ROTATION ON A VERTICAL OR HORIZONTAL HEART

When clockwise rotation is extreme, the back of the heart can actually face the anterior surface of the right chest.[1] In such a case Lead V_1 and even Lead V_2 may show the pattern of the back of the heart, namely, a QR or a qR and a downward T. Figure 5 shows such a tracing, that of a patient with cor pulmonale. Precordial Leads V_{2-6} in this case show normal RS patterns.

When such extreme clockwise rotation is present, Lead aVR not only shows a QR type of pattern, but the R becomes tall with respect to the q. Although this qR pattern in Lead aVR has been interpreted as a sign of right ventricular hypertrophy,[5] actually it is merely a sign of extreme clockwise rotation and may occur in cases not only of right ventricular hypertrophy but myocardial infarction and even in normal people. Although extreme clockwise rotation with a qR in Lead V_1, can theoretically occur normally, I have not seen it in any normal person.

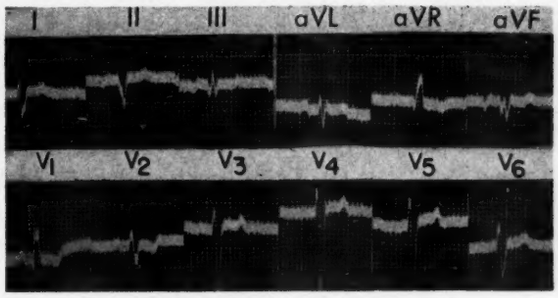

FIG. 5. The effect of extreme clockwise rotation on the heart; a patient with cor pulmonale.

CONCLUSIONS

1. Precordial leads as well as unipolar extremity leads and standard leads vary when clockwise rotation of the heart occurs.
2. When marked clockwise rotation of the heart occurs, precordial Leads V_1 through V_5 or V_6 may face the epicardial surface of the right ventricle and show rS and RS patterns. This may occur in a normal person with a vertical or horizontal heart, or in patients with right or left ventricular hypertrophy.
3. A further sign of marked clockwise rotation is the development of a QR, Qr or qR pattern in Lead aVR.
4. When extreme clockwise rotation is present, precordial Lead V_1 and sometimes Lead V_2 can also face the back of the heart and show a QR or qR pattern in addition to Lead aVR.

REFERENCES

1. GOLDBERGER, E. The differentiation of normal from abnormal Q waves. *Am. Heart J.*, 30: 341, 1945.
2. GOLDBERGER, E. and SCHWARTZ, S. P. The electrocardiogram in chronic pulmonary disease. *Am. Rev. Tuberc.*, 53: 34, 1946.
3. GOLDBERGER, E. Unipolar Lead Electrocardiography. 2nd ed. Philadelphia, 1949. Lea & Febiger.
4. GARDBERG, M. and ASHMAN, R. The QRS complex of the electrocardiogram. *Arch. Int. Med.*, 72: 210, 1943.
5. MYERS, G. B., KLEIN, H. A. and STOFER, B. E. The electrocardiographic diagnosis of right ventricular hypertrophy. *Am. Heart J.*, 35: 1, 1948.

Electrocardiographic Evaluation of Boeck's Sarcoid and Advanced Pulmonary Tuberculosis*

Special Reference to Interpretation of the Multiple Unipolar Leads

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INTERPRETATION of multiple unipolar leads recorded in patients with pulmonary manifestations of Boeck's sarcoid revealed the frequent occurrence of left ventricular hypertrophy, an electrocardiographic finding which may prove to be of added value in the differentiation of sarcoidosis and tuberculosis. Sarcoidosis is a systemic disease which may involve the myocardium and account for electrocardiographic irregularities[1–4] while tuberculosis rarely involves the myocardium directly and electrocardiographic abnormalities, when present, are of different form than those observed in sarcoid. The pulmonary roentgenographic changes of sarcoidosis and tuberculosis frequently resemble each other and in many cases offer a diagnostic problem of some magnitude.

METHOD AND MATERIAL

Serial teleoroentgenograms and electrocardiograms in seven cases of Boeck's sarcoid and twenty cases of far advanced pulmonary tuberculosis were compared. The electrocardiograms were recorded by using a modified central terminal[5] and included leads aV_L, aV_F, V_1, V_2, V_3, V_4, V_5 and V_6, in addition to limb leads I, II and III. The positions explored were those specified by the Committee of the American Heart Association for the Standardization of Precordial Leads.[6]

RESULTS

Of the seven patients with Boeck's sarcoid six gave electrocardiographic findings which were interpreted as definite evidence of left ventricular hypertrophy. One had a normal electrocardiogram. Teleoroentgenograms of five of these subjects revealed diffuse areas of infiltration scattered throughout both lung fields. One revealed a nodular enlargement of the mediastinum. A positive diagnosis was established in each case by microscopic examination of lymph node biopsies after exhaustive studies failed to show evidence of acid-fast organisms.

The electrocardiograms of twenty patients with far advanced pulmonary tuberculosis showed the following:

No. of Cases	Diagnosis
3	Incomplete right bundle-branch block
3	Pericarditis
2	Right ventricular hypertrophy
1	Moderately recent anteroseptal infarction
11	Normal

Teleoroentgenograms showed bilateral disease with cavitation in most instances and the sputum contained acid-fast organisms in each case.

ELECTROCARDIOGRAMS ILLUSTRATING CHANGES

Two months after the diagnosis of Boeck's sarcoid was made in a colored male, aged twenty-three, the electrocardiogram in Fig-

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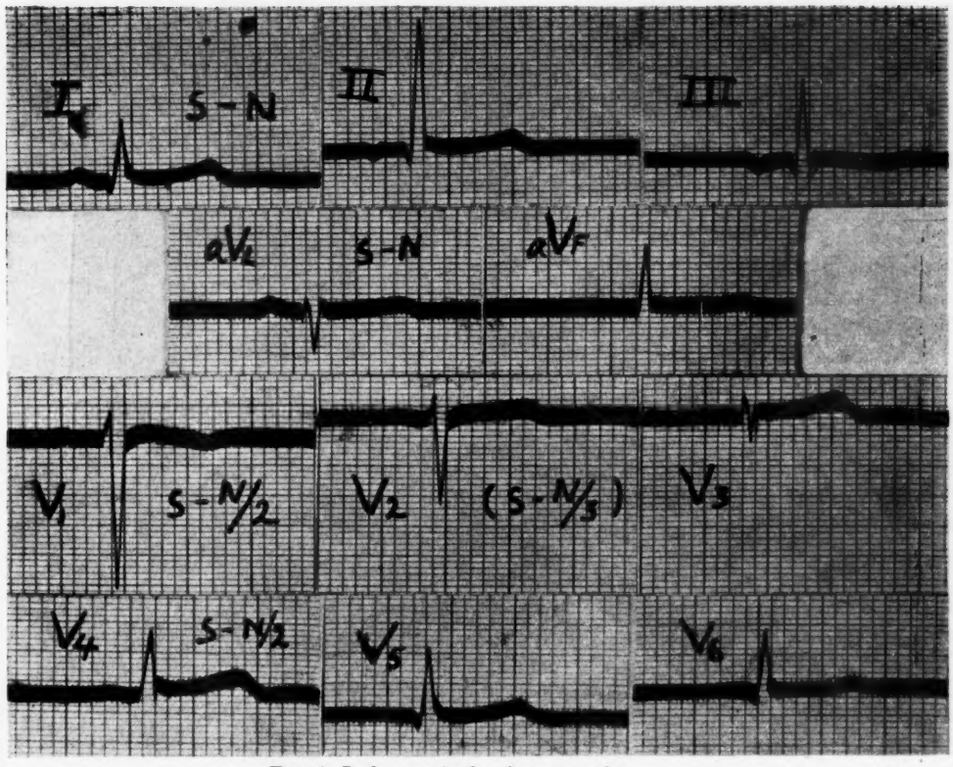

FIG. 1. Left ventricular hypertrophy.

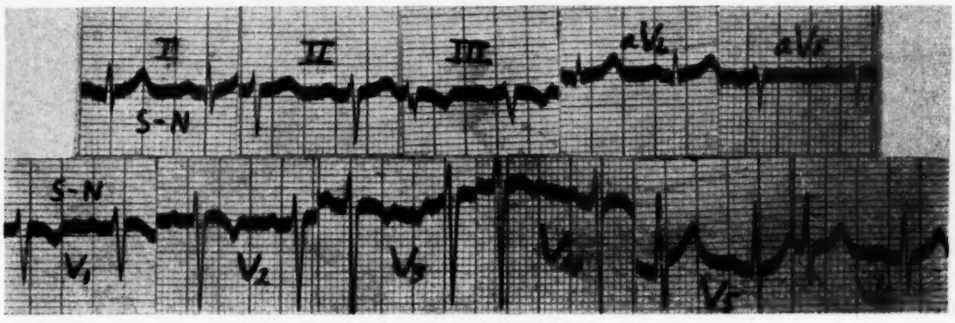

FIG. 2. Pericarditis.

ure 1 was recorded. The patient presented no subjective or objective clinical findings when a routine chest roentgenogram first indicated disease. Repeated sputum and gastric studies were negative for acid-fast organisms. The blood pressure was 120/80. Leads V_1 and V_2 which represent potential variations from the free surface of the right ventricle were recorded as one-half and one-third the normal sensitivity, respectively, and show a prominent S. Transition occurs at V_3, following which there is a prominent R at V_5 and V_6 representing the potential variations of the left ventricle. The changes are diagnostic of left ventricular hypertrophy; the heart is in the vertical position and the mean electrical axis of QRS (A_{QRS}) is normal. Six of the seven patients with Boeck's sarcoid presented similar changes.

The electrocardiogram reproduced in Figure 2 was recorded in a white man, aged twenty-four. The initial diagnosis of pulmonary tuberculosis was established eighteen months earlier and marked progression followed. The T wave is positively spiked in lead I and inverted in lead III. The RS-T segment is arched upward and T shows a late inversion in V_1, V_2, V_3 and V_4. Transition is not complete at V_6. The changes are

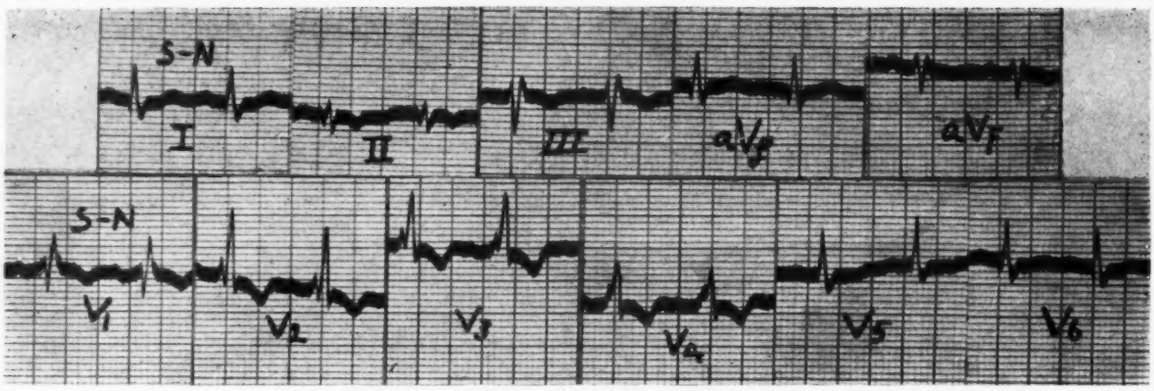

FIG. 3. Right bundle branch block.

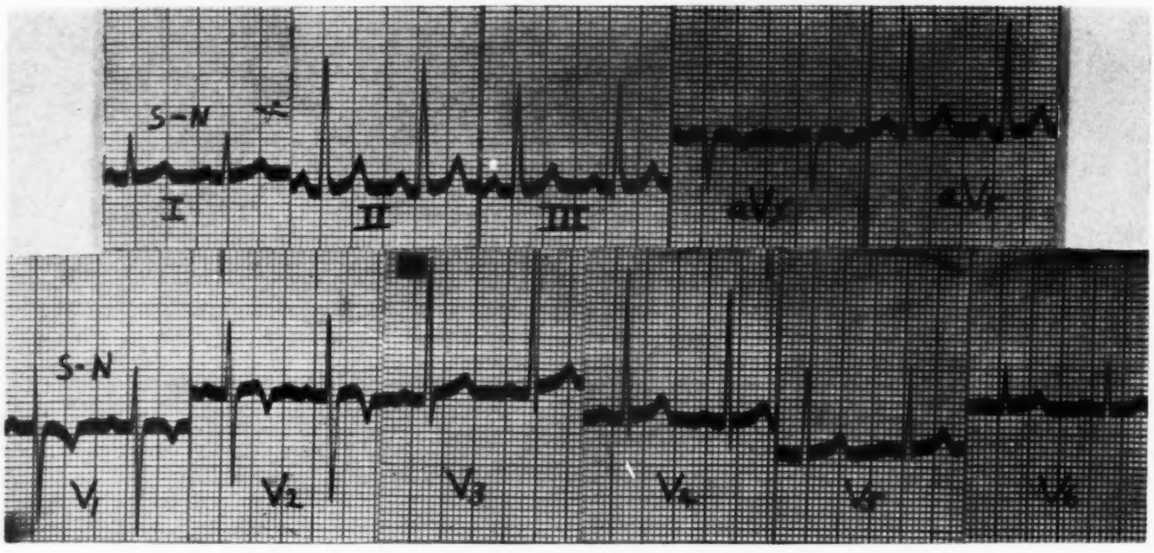

FIG. 4. Right ventricular hypertrophy.

compatible with chronic, low grade pericarditis; the heart is in the horizontal position and there is a counterclockwise rotation of A_{QRS} (left axis deviation).

The electrocardiogram which is reproduced in Figure 3 was recorded in a white man, aged thirty, in whom a diagnosis of far advanced pulmonary tuberculosis had been established by positive sputum and gastric washings and chest roentgenographic changes. The QRS interval is 0.12 seconds and the S is broad in lead I. R and R′ deflections are present in leads aV_F, V_1, V_2 and V_3. Transition occurs between V_4 and V_5; V_5 and V_6 are contributions to the precordium from the left ventricular surface and show a broad S. The heart is in the horizontal position and there is a counterclockwise rotation of A_{QRS}. When the right branch of the His bundle is blocked, accession of the interventricular septum from the left branch produces an initial positive potential at the surface of the right ventricle whereas late accession of the free wall of the right ventricle produces a second positive variation at this surface late in the QRS interval. These two positive variations undoubtedly exert a dominant effect in the formation of R and R′ in leads aV_F, V_1, V_2 and V_3.[7–9]

The electrocardiogram (Fig. 4) was recorded in a white man, aged twenty, who had shown a slowly progressive disease for two years. Sputum and gastric washings were positive for acid-fast organisms and the chest roentgenogram revealed exudative disease with cavitation. R is prominent at V_1 and V_2 where T is rounded and shows a

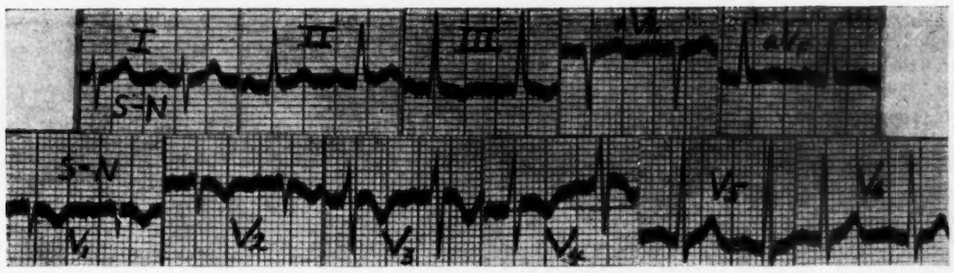

FIG. 5. Anteroseptal infarction.

terminal negative deflection. Transition occurs between V_2 and V_3. V_3, V_4, V_5 and V_6 are the potential variations transmitted to the precordium from the surface of the left ventricle. These changes suggest right ventricular hypertrophy, the heart in the vertical position and a tendency toward clockwise rotation of A_{QRS}.

The electrocardiogram (Fig. 5) was recorded in a white male, aged thirty-four, one year following the initial diagnosis of pulmonary tuberculosis and two weeks following an attack of precordial pain which radiated to his left shoulder and was accompanied by dyspnea and orthopnea. Sputum and gastric washings were positive for acid-fast bacilli and the teleoroentgenogram revealed far advanced pulmonary disease. R is minute in leads aV_L, V_1 and V_2 and is low with a slurred upstroke in V_3. T is inverted in leads V_1, V_2, V_3 and V_4. In view of the history and these changes a diagnosis of moderately recent anteroseptal infarction appears justified; the heart is in the vertical position and there is clockwise rotation of A_{QRS}. Characteristically, when precordial lead changes are confined to V_1, V_2 and V_3, little or no change is present in the limb leads.

COMMENTS

Sarcoidosis is considered to be a systemic disease in which no organ is exempt from possible involvement. Schaumann, in his initial publication,[10] described sarcoid involvement of the myocardium in postmortem material. His observation has been confirmed on numerous occasions and various electrocardiographic conduction irregularities have been reported.[1–4] Unipolar chest leads were not employed in these observations, however, and consequently the repeated finding of left ventricular hypertrophy in these cases is of interest. Why the left ventricle is selectively involved is unexplained. Perhaps sarcoidosis, like rheumatic fever, has a tendency to localize in the heart with an intensity which is proportional to the work done.

As a general rule pulmonary tuberculosis is unaccompanied by changes in the electrocardiogram unless there is involvement of the pericardium. In far advanced pulmonary disease secondary myocardial changes may occur and account for secondary alterations in the heart's electrical field. It was for this reason that patients with far advanced pulmonary tuberculosis were selected for this study. Of twenty patients only five presented abnormal curves which could be attributed to pulmonary disease.

SUMMARY

1. Left ventricular hypertrophy produced by Boeck's sarcoid can be detected in the precordial electrocardiogram.

2. A few patients with sarcoidosis presented electrocardiographic changes which differed from those encountered in a group of twenty patients with far advanced pulmonary tuberculosis. These differences, if equally consistent in larger groups, might prove helpful diagnostic leads.

Acknowledgment: An expression of thanks is extended to Dr. Robert H. Bayley for helpful criticism in the preparation of this manuscript.

REFERENCES

1. LONGCOPE, W. T. and FISHER, A. M. The effect of Schaumann's disease upon the heart and its mechanism. *Acta med. Scandinav.*, 108: 529, 1941.

2. Longcope, W. T. and Fisher, A. M. Involvement of the heart in sarcoidosis or Besnier-Boeck-Schaumann's disease. *J. Mt. Sinai Hosp.*, 8: 784, 1942.
3. Johnson, J. B. and Jason, R. S. Sarcoidosis of the heart—report of a case and review of the literature. *Am. Heart J.*, 27: 246, 1941.
4. Salvesen, H. A. The sarcoid of Boeck, a disease of importance to internal medicine. *Acta med. Scandinav.*, 86: 127, 1935.
5. Goldberger, Emanuel. A simple, indifferent, electrocardiographic electrode of zero potential and a technique of obtaining augmented, unipolar, extremity leads. *Am. Heart J.*, 23: 483, 1942.
6. Supplementary Report by the Committee of the American Heart Association for the Standardization of Precordial Leads. *Am. Heart J.*, 15: 235, 1938.
7. Wilson, F. N., Johnston, F. D. and Barker, P. S. Electrocardiograms of an unusual type in right bundle-branch block. *Am. Heart J.*, 9: 472, 1934.
8. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cortrim, N., DeOliveira, R. M., Scarsi, R. and Barker, P. S. The precordial electrocardiogram. *Am. Heart J.*, 27: 19, 1944.
9. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F. and Barker, P. S. On Einthoven's triangle, the theory of unipolar electrocardiographic leads, and the interpretation of the precordial electrocardiogram. *Am. Heart J.*, 32: 277, 1946.
10. Schaumann, J. Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings. *Brit. J. Dermat.*, 48: 399, 1936.

Hemiplegia Attending Acute Myocardial Infarction*

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OCCASIONAL reorientations in medical thought are useful goads against the dogma which too readily encases our ideas in fixed mental habits. It is usually taken for granted that such an episode as hemiplegia occurring at the time of acute myocardial infarction or shortly after is embolic in origin, the embolus in question coming from a ventricular mural thrombus. Some years ago, in surveying a large series of cases of myocardial infarction proved at autopsy, it was noted that the majority of cases of hemiplegia which followed infarction of the heart were associated with cerebral arteriosclerosis and local thrombosis or even hemorrhage rather than with emboli.[1] Still later, in association with Read[2] one of us (W. B. B.) reported several instances of hemiplegia as the presenting symptom of acute myocardial infarction. There was advanced arterial disease of the brain but no acute lesion of the cerebral arteries to account for the major symptoms. It was suggested that the reduction in blood flow, affecting particularly the cerebral foci with the most severely diseased arteries, determined the clinical picture. This striking masquerade of coronary thrombosis with a neurologic debut has not aroused the interest of cardiologists or caught the attention of internists though it is better known to some neurologists.[3] It is, however, sufficiently important that its recognition not be confined to those isolating themselves in any medical specialty.

It is impossible to prove the nature of this type of case except by postmortem study of heart and brain. It is possible, indeed probable, that less serious cases of like nature occur. In an attempt to discover them clinically we have taken electrocardiograms in many patients admitted to the hospital with hemiplegia. In several patients not included in this study the medical history revealed that hemiplegia had ensued shortly after cardiac infarction. In only one such case was the diagnosis proved. The others either recovered or died and no autopsy was performed.

At times there is difficulty in assigning an exact time to the onset of an acute myocardial infarct.[1] In the instances we are reporting the lesion in the heart gave testimony of an age in keeping with the known time of collapse or pain which we have used as the clinical landmark indicating the acute onset of myocardial infarction.[4] The present study casts no light on the possibility that hemiplegia from cerebral hemorrhage or thrombosis, and hyperactivity or convulsions associated with it might themselves precipitate coronary thrombosis or myocardial infarction. The absence of the acute lesion, cerebral thrombus or hemorrhage in our cases indicates that the central nervous system was not primarily concerned but manifestations referable to it were concomitants or early sequelae of the acute myocardial infarction.

We have reviewed the protocols of all autopsies done in the Department of Pathology for the years 1941 through 1946 to look for cases in which hemiplegia was precipitated by acute myocardial infarction. We set up as criteria for selection the presence of (1) a gross recent infarct of the heart measuring at least 3 by 3 cm. and (2) focal neurologic signs suggesting cerebral

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hemorrhage, thrombosis or embolus but the (3) absence of any gross evidence of an acute vascular lesion of the cerebral vessels. The six cases discussed in this report were found. Pronounced arteriosclerosis of the larger cerebral vessels was present. It has been the experience of some pathologists that emboli and thrombi are overlooked unless special precautions are taken to find them. An injection plus dissection of the arteries supplying the brain would have given assurance that there were indeed no acute vascular lesions of larger cerebral arteries but such a procedure was not carried out. While no rigid technic was followed, emboli, thrombi or hemorrhage were sought specifically because of the clinical diagnosis of hemiplegia. It is unlikely that any lesion of major importance was missed although the possibility exists.

Some cases had to be discarded because the autopsy had not included examination of the brain. There are other examples of cardiac origin for non-embolic hemiplegia, including such different diseases as aortic stenosis, dissecting aneurysm[5,6] and rupture of a syphilitic aneurysm; all without acute vascular lesions of major cerebral vessels but with pronounced cerebral arteriosclerosis. Clinical evidence in some instances, especially in which transient hemiplegia occurred in aortic stenosis, demonstrated a relationship between the neurologic crisis and a fall in arterial blood pressure; in other cases this mechanism was suspected but not proved. An analogy between the physiologic disturbance of this condition and the syndrome of sensitive carotid sinus may exist.

REVIEW OF THE LITERATURE

Bean and Read[2] in 1942 called attention to a syndrome of hemiplegia attending acute myocardial infarction with the neurologic signs and symptoms overshadowing the acute cardiac disorder. They pointed out that hemiplegia and acute infarction of the heart occurring in the same patient might be (1) independent of each other, (2) the cerebral disorder might be an embolic sequel of dislodging a ventricular mural thrombus or (3) shock resulting from the acute cardiac disorder might be associated with cerebral ischemia, especially when arteriosclerosis of vessels in the brain was advanced, and thus produce hemiplegia. The resulting symptoms and signs were thought to have been determined by the focal pattern of vascular sclerosis in the cerebral arteries. In a review of medical papers related to this topic no proved instances of hemiplegia after myocardial infarction without embolism were found, although there were numerous observations that other acute cardiac episodes might be associated with transitory palsies and paralyses. Since this paper there has been scant notice of the problem. Cookson[7] emphasized fits and faints as signs of cardiac infarction and commented on the old age and poor prognosis of his patients. He believed that reflex bradycardia was more important than hypotension in the production of syncope, but disease in cerebral vessels was considered to be another factor. Race and Lisa[8] found that 15 per cent of 100 autopsied cases of myocardial infarction had lesions of cerebral vessels. For the most part in those with central nervous system lesions the cardiac disease had not been diagnosed. There were indeed five cases in which the only acute vascular lesion was coronary thrombosis but the neurologic aspects of the signs and symptoms had indicated only hemiplegia and presumably the mechanism was the same as reported by others.[2] Fisher and Zukerman[9] found three cases of cerebral hemorrhage and two of cerebral thrombosis in 108 cases of myocardial infarction but did not discuss the time relationship of the episodes or the accuracy of the clinical diagnosis.

Four mechanisms for the production of hemiplegia following acute myocardial infarction may exist. *Embolism*, *thrombosis* and *hemorrhage* have been noted fairly often, but *ischemia* most pronounced in regions whose arterial supply is reduced by arteriosclerosis may be another important factor.[2] There

are certain common time sequences which should suggest which of these mechanisms is responsible for hemiplegia in a given instance if the train of events is known from an accurate history, which may be difficult or impossible to learn in a patient with a stroke. If hemiplegia has its onset at the same time or shortly after the acute cardiac infarction as a syncopal or apoplectic seizure while shock is prominent, the usual mechanism is cerebral ischemia and hypoxia. When its onset is somewhat later, after the first few hours but usually within the first few days up to a week, a large cerebral vessel may have become occluded by a thrombus or cerebral hemorrhage may have occurred as a result of sustained vasoparalysis.[10] Evidence has been adduced that following acute myocardial infarction there may be an abnormal tendency for blood to clot rapidly.[11] After the first week an embolus from a mural thrombus on the endocardial wall may lodge in the brain and suddenly cause hemiplegia. Those divisions of time are not absolute. Recurring shock may follow acute myocardial infarction and give rise to hemiplegia, or an embolus from an auricular thrombus may become detached soon after acute cardiac infarction. In general the correct clinical diagnosis can be suspected if the time relationship of hemiplegia and infarction of the heart is known.

The vasotonic and physical forces which maintain the dynamics of cerebral blood flow have been the subject of much study but many aspects of the problem are not yet clearly understood. Aring[3] has given a comprehensive and critical review of the physiologic control of cerebral circulation. Extracerebral factors are recognized as most important in governing intracerebral blood flow. There are, however, relatively weak neurovascular mechanisms, and humoral factors such as CO_2, pH changes and chemical agents may affect vessel caliber and blood flow. Villaret and Cachera[12] studied the effects of emboli in the form of particulate matter introduced into the cerebral circulation, and through skull windows were able to observe venous engorgement and hemorrhagic infarction. A clue to possible mechanisms in our own cases and the close connection between cerebral hemorrhage and thrombosis is found in Scheinker's[10] observation on vasoparalysis and the ensuing vasothrombosis. He found that as a result of such varied stimuli as physical trauma, sulfonamide intoxication, carbon monoxide poisoning and arsenical encephalopathy the brain might be injured gravely. By histologic study he traced the changes from vasodilatation through vasoparesis to vasoparalysis leading to stasis, diapedesis and finally to the coalescence of many minute hemorrhages. Presumably an even earlier stage in his cases may have been vasoconstriction so intense or so sustained that the resulting hypoxia led to changes in vascular endothelium.

Since some of our autopsy material has been found to manifest similar vascular changes, we suggest that the phenomenon of hemiplegia may be initiated by a fall in arterial blood pressure associated with the early state of myocardial infarction. Cerebral arteries with enough organic obstruction to reduce the blood flow critically may determine the area or areas most severely affected. If anoxia continues long enough, alterations of the walls of small vessels may permit the escape of blood. By the coalescence of many small hemorrhages a large infarct may be formed. If, however, shock is not of sufficient duration or intensity, vascular alterations may not be demonstrable even though cerebral cell function or structure may be disordered. Indeed there is presumably a stage at which complete recovery is possible, and we have observed cases clinically in which this situation was suspected although it could not be proved.

There is little in the way of therapy which can be suggested for the cerebral disturbance. If it is realized that the neurologic changes may be reversible, however, the customary nihilistic attitude toward hemiplegia may change to a more opti-

mistic one, even though the prognosis may still be none too good with an acute cardiac infarct. Where shock associated with an acute myocardial infarct causes local or general neurologic signs apparently of primary cranial origin, the correct interpretation may be vital to the management of the patient. If it is possible to improve the function of the heart and if this is done early, the stroke may disappear rapidly and an apoplexy apparently disastrous may prove transitory. Since it is not possible to make a definitive diagnosis of this cerebral masquerade of acute cardiac infarction without anatomic proof, the most that can be expected in the diagnosis of non-fatal examples of this syndrome is a properly guided suspicion which will direct treatment toward the heart rather than the head.

The following brief case reports include all proved cases of this syndrome which have come to autopsy since our earlier report.[2] The pathologic findings are outlined in Table I.

CASE REPORTS

CASE I. C. V., a seventy year old white man, was admitted to the Neurology Service on February 26, 1944, having collapsed at home. He had slept after dinner and upon awakening had gone to the toilet because he felt nauseated. There he vomited. Pallor, weakness and profuse perspiration occurred and he fainted. He had complained of no pain before he lost consciousness.

Physical examination revealed the temperature to be 101°F., pulse 80, respirations 28, blood pressure 230/110. The patient was a plethoric old man, stuporous and had difficulty with respiration. He demonstrated purposeless involuntary movements and was unresponsive. He showed no signs of heart failure. The heart was enlarged and a systolic murmur was heard at the apex. There was left facial weakness, symmetrical hyperreflexia and bilateral Babinski signs.

Laboratory findings were as follows: the erythrocyte count was 4.9 m.; leukocyte count 5,800; hemoglobin 15 Gm.; blood urea nitrogen was 16 mg. per 100 cc.; urine examination was normal. Lumbar puncture revealed normal pressure, negative Pandy test, 20 red blood cells and 1 white blood cell per cu. mm. The cerebrospinal fluid protein was 40 mg. per 100 cc.

He died eleven hours after admission following a progressive downhill course. The clinical diagnoses were cerebral hemorrhage and hypertensive cardiovascular disease.

CASE II. F. W., an eighty-two year old white man, was admitted to the Neurology Service on June 15, 1944, having collapsed at home where he was found conscious on the floor but unable to move because of a left hemiparesis. Before falling he had been dizzy.

Physical examination revealed the temperature to be 101.2°F., pulse 120, respirations 30, blood pressure 125/80. The patient was an alert, acutely ill man with left hemiparesis but no evidence of heart failure. Breath sounds were stertorous so the heart sounds were obscured. A Kernig sign was elicited; there was hyporeflexia and swallowing was difficult.

Laboratory data were as follows: erythrocytes 5.05 m.; leukocytes 16,550; hemoglobin 14.3 Gm., no urine was collected. Lumbar puncture was normal with the cerebrospinal fluid protein 22 mg. per 100 cc.; blood urea nitrogen 65 mg. per 100 cc.; blood Kahn was negative.

Fluids were aspirated and respiratory distress increased. He died two days after admission. The diagnoses were thrombosis of the right middle cerebral artery and pneumonia.

CASE III. W. B., a seventy-one year old white man with a history of anginal attacks, was admitted to the Medical Service on February 4, 1946, because of marked respiratory difficulty. One week before admission the patient had become ill, vomited, was weak and became dyspneic. There was chest pain with the attack. He became especially weak on the left side after the acute attack but the exact time when hemiplegia occurred could not be learned.

During physical examination pulse and blood pressure readings were not obtainable; respirations were 45. He was cyanotic and dyspneic and coarse rhonchi obscured the heart sounds. The left arm and leg were not moved; the patient puffed out his left cheek with respirations and no reflexes could be elicited on the left.

No blood count was taken or urinalysis performed. Postmortem cisternal puncture yielded normal cerebrospinal fluid with 5 lymphocytes per cu. mm.; blood urea nitrogen was 20 mg. per 100 cc.

He died one hour after admission. Diagnoses were acute myocardial infarction with left hemiplegia, probably due to embolus.

TABLE I

Age	Sex	Race	Heart										Peripheral Infarcts	Brain					
			Weight (Gm.)	Coronary Arteries				Infarcts		Mural Thrombus									
				Arteriosclerosis	Left Anterior Descending	Circumflex	Right	Healed	Recent	Auricular		Ventricular			Weight (Gm.)	Arteriosclerosis	Thrombosis or Hemorrhage	Infarct	Edema	Atrophy	Horizontal Section
										Right	Left	Right	Left							
70	M	W	470	2+	Patent	Patent	Patent	0	Septum and parts of left ventricle	0	0	0	0	0	.....	4+ with elevated plaques	Petechiae and 1 small hemorrhage in left frontal lobe, no gross thrombus	0	0	0	Petechiae and 1 small hemorrhage in left frontal region
82	M	W	435	3+	Narrow	Narrow	Narrow	Tip of apex and posterior wall of left ventricle	Surrounding old one	0	0	0	Large	0	1,365	3+ with elevated plaques	0	0	0	2+	Atrophy with enlarged ventricles
71	M	W	475	3+ with ulcerated plaques	Narrow	Narrow	Narrow	Apex and anterior lateral wall left ventricle	Apex, anterior wall, left ventricle and septum	0	0	0	Large	0	1,190	1+	Congestion and small petechiae in corona radiata, no gross thrombus	0	3+ right frontal	1+ focal	Focal atrophy, some swelling, congestion petechiae
77	F	W	500	4+	Narrow	Thrombosis and marked stenosis	Thrombosis and marked plaque formation	0	Posterior left ventricle	0	0	0	0	0	1,320	3+ with elevated plaques	0	0	1+ left parietal region	0	Slight congestion of basal ganglia and brain stem
77	M	W	375	3+ with plaques	Occluded	Narrow	Narrow	0	Septum and anterior, lateral and posterior wall left ventricle	0	0	0	Large	0	1,365	1+	0	0	1+ bilateral	0	Slight swelling in parietal region
68	F	C	335	4+ with a few plaques	Narrow	Narrow	Narrow	0	Anterior and inferior parts of septum and anterior wall of left ventricle	0	0	0	0	0	.....	3+	0	0	1+ white matter	0	Slight swelling of white matter

CASE IV. M. B., a seventy-seven year old white woman, was admitted to the Neurology Service on April 21, 1946, after having been found on the floor at home.

Physical examination showed: pulse 100, respirations 36, blood pressure 85/65. She was very dyspneic. Coarse rhonchi obscured the heart sounds. Both arms were flaccid but tendon reflexes were retained while the legs were moved on noxious stimulation but were areflexic. Corneal reflexes were absent.

Laboratory data were as follows: red blood cells 4.82 m.; white blood cells 4,750; hemoglobin 14 Gm. Urine showed 2+ albumin and occasional white blood cells; blood urea nitrogen 24 mg. per 100 cc. Wassermann reaction was negative. Lumbar puncture was normal with a cerebrospinal fluid protein of 43 mg. per 100 cc. An electrocardiogram was interpreted as left ventricular preponderance and probable anterior myocardial infarction.

Death occurred three hours after admission. Diagnoses before the electrocardiogram was taken were cerebral hemorrhage or thrombosis, acute pulmonary edema and possible myocardial infarction.

CASE V. G. S., a seventy-seven year old white man, was admitted to the Medical Service on March 18, 1947, after becoming delirious following a sudden collapse. His pulse was 40, respirations 14 and blood pressure 75/40. The patient had Cheyne-Stokes respirations. Both lungs were filled with coarse rhonchi and wheezes. No cardiac enlargement was detected. Heart rhythm was periodically irregular and heart sounds were distant. The right arm and leg were spastic. Reflexes were increased in the arms and absent in the legs and there was a Babinski sign on the right.

Laboratory data were as follows: red blood cells 5.27 m.; white blood cells 15,200 with 93 per cent polymorphonuclears. Urine showed 2+ albumin, occasional white blood cells and 2 to 3 red blood cells per high power field; blood urea nitrogen 60 mg. per 100 cc. An electrocardiogram showed complete A-V dissociation with idioventricular rhythm.

Therapy included sedation, plasma and fluids. Soon after admission he went into peripheral circulatory failure, became confused and developed a left hemiparesis, weakness and acute respiratory distress. He died forty-two hours after admission. The diagnoses were myocardial infarction, cerebral vascular accident and hypostatic pneumonia.

CASE VI. K. C., a sixty-eight year old colored woman, was seen in the Receiving Ward on April 18, 1947, after having collapsed on the street. She had been treated in the Outpatient Department for hypertension and heart failure of long duration. Pulse was 100, respirations 30, blood pressure 70/?. She was semicomatose and showed fine convulsive movements of the right arm, neck and face. There was an abrasion of the left temple. She did not move her left arm or leg and showed weakness of the left face. Reflexes were of no localizing value. Respirations were very labored during the dyspneic phase of her Cheyne-Stokes breathing. Basal rales and wheezes were prominent in the chest. The heart was enlarged with sinus rhythm and premature beats but no murmurs, friction rubs or gallop rhythm. Neck vein distention was notable and the liver extended 3 fingersbreadth below the right costal margin. Ankle edema was absent.

No blood count was taken. The urine showed rare white blood cells. Lumbar puncture showed initial pressure of 220 mm. of water with no change in pressure after removal of 7 cc. of fluid. There were 48 red blood cells and 7 white blood cells per cubic mm. and the cerebrospinal fluid protein was 47 mg. per 100 cc., blood urea nitrogen 21, sugar 294 per 100 cc., CO_2 20.5 volumes per cent. Lateral skull films suggested a fracture in the region of the left lambdoidal suture. An anteroposterior chest film showed an enlarged heart.

Intravenous fluids were started and stimulants given but she died shortly after arriving at the hospital. Diagnoses were hypertensive cardiovascular disease with cardiac insufficiency, possible myocardial infarction, probable encephalomalacia in right internal capsule and possible subdural hematoma.

COMMENT

Our experience with a type of stroke which attends the early phases of acute myocardial infarction has been outlined. In this hospital it has constituted an important although relatively uncommon problem. The diagnosis is often missed because clinicians who see this type of patient are not aware that the cause of "apoplexy" can be other than thrombus, embolus or hemorrhage. It is evident from a survey of pertinent medical papers[2,7,8] that many disturbances of cardiac function such as

paroxysmal arrhythmias, acute left ventricular failure, shock and postural hypotension may be attended by hemiplegia which may be as transitory as the provoking disturbances in the heart or may persist after the heart resumes more nearly normal function. In addition to the clear-cut entity of hemiplegia it is probable that in at least some instances confusion, coma, delirium, fainting and convulsions which may usher in, attend or follow shortly upon the acute episode of myocardial infarction, depend on the reduction in blood flow which affects the cerebral tissues according to the degree and locus of disease in the arteries supplying the brain. Reflexes may also have a part in the disturbance in cerebral blood flow but this remains a speculation. Luminal changes or spasm of sclerotic or calcified vessels could hardly reach major proportions.

In some of the brains in the present series of cases the changes found are characteristic of the vasoparalysis described by Scheinker.[10] It is believed that the ensuing deterioration of brain cells is adequate to account for the continuation of hemiplegia until death. In probable instances of this kind in which hemiplegia is fleeting, recovery leaves the exact diagnosis in doubt but some of the rapidly clearing strokes may be of this nature. In the occasional instance in which transient hemiparesis is repeated in a recurring pattern the clinical picture may be explained by restricted blood flow through a diseased cerebral artery rather than vascular spasm in a "sensitized" or conditioned artery. Systemic hypoxia associated with heart failure and pulmonary congestion may aggravate an already serious condition and further the disintegration which finally causes death.

CONCLUSIONS

Clinical and morphologic data have been presented in six patients with major symptoms of acute cerebral disturbance associated with recent infarction of the heart. In all but two a myocardial infarct was suspected clinically.

Suggestive evidence has been advanced that the pattern of local arterial disease in the brain determined the clinical signs and symptoms. A reduction of cardiac output following infarction of the heart thus may lead to the clinical masquerade of an acute cerebral vascular accident.

If the hypodynamic state is severe enough or lasts long enough, vasoparesis, vasoparalysis and coalescing small hemorrhages may occur.

The syndrome has received little attention. If properly identified and treated, there is some chance that one form of "stroke" will warrant a more optimistic outlook.

REFERENCES

1. Bean, W. B. Infarction of the heart. II. Symptomatology of acute attack. *Ann. Int. Med.*, 11: 2086, 1938.
2. Bean, W. B. and Read, C. T. Central nervous system manifestations in acute myocardial infarction. *Am. Heart J.*, 23: 362, 1942.
3. Aring, C. D. Vascular diseases of the nervous system. *Brain*, 68: 28, 1945.
4. Mallory, G. K., White, P. D. and Salcedo-Salgar, J. The speed of healing of myocardial infarction. *Am. Heart J.*, 18: 647, 1939.
5. Wood, F. L., Pendergrass, E. P. and Ostrum, H. W. Dissecting aneurysm of the aorta with special reference to its roentgenographic features. *Am. J. Roentgenol.*, 28: 437, 1932.
6. Baer, S. and Goldburgh, H. L. The varied clinical syndromes produced by dissecting aneurysm. *Am. Heart J.*, 35: 198, 1948.
7. Cookson, H. Fainting and fits in cardiac infarction. *Brit. Heart J.*, 4: 163, 1942.
8. Race, G. A. and Lisa, J. R. Combined acute vascular lesions of brain and heart, a clinico-pathologic study of 15 cases. *Am. J. M. Sc.*, 210: 732, 1945.
9. Fisher, R. L. and Zukerman, M. Coronary thrombosis. *J. A. M. A.*, 131: 385, 1946.
10. Scheinker, I. M. Vasoparalysis of the central nervous system, a characteristic vascular syndrome significance in the pathology of the nervous system. *Arch. Neurol. & Psychiat.*, 52: 43, 1944.
11. Ogura, J. H., Fetter, N. R., Blankenhorn, M. A. and Glueck, H. I. Changes in blood coagulation following coronary thrombosis measured by the heparin retarded clotting test (Waugh and Ruddick test). *J. Clin. Investigation*, 25: 586, 1946.
12. Villaret, M. and Cachera, R. Les Embolies Cerebrales. P. 133. Paris, 1939. Masson et Cie.

Review

The Role of Allergy in the Pathogenesis of Rheumatic Fever*

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AFTER a half century of clinical observation and investigation the group A hemolytic streptococcus has been well established as the causative agent of the great majority of cases of rheumatic fever, a preceding streptococcus infection having been documented by numerous methods. However, the mechanism by which streptococcal infection brings about the disease state, rheumatic fever, is still obscure. This discussion will be concerned with one of the suggested etiologic mechanisms, that pertaining to bacterial allergy. Many of the factors which have been thought to participate in the genesis of rheumatic disease are considered in their relationships to the biochemical, immunologic and pathologic aspects of known allergic processes.

THE HOST

As with many diseases which attack with some degree of discrimination rather than haphazardly as does a wild contagion, rheumatic fever appears to occur in individuals predisposed by some feature of their constitution. The incidence of multiple cases in a family is sufficiently common to suggest that this feature is probably hereditary.[62,199,212,280] Wilson and her coworkers have applied classical technics of genetic analysis to this problem. They calculate that the predisposition to rheumatic fever occurs in 5 per cent of the population and that it is inherited through a single autosomal gene, as a Mendelian recessive characteristic. However, the possibility that similar environmental factors may be exerted, even through a number of generations, has not been excluded and, indeed, has been suggested by many studies.[180,199,212] Wilson[280] states "Final conclusions on the role of environment do not appear possible until data are available on the familial incidence of rheumatic fever among the well-to-do."

The characterization of a predisposed constitution does not exclude the possibility that individuals ordinarily not predisposed and with no family stigmata may nevertheless exhibit the same pathologic reaction under unusual circumstances. Epidemics of rheumatic fever have been described in which from 10 to 30 per cent of individuals with an acute tonsillitis developed acute rheumatic fever.[18,59,93,288] Such epidemics were particularly well documented at training camps during the recent war, and are of special interest because many of the known rheumatics had been disqualified from service.[211,259,271] Holbrook[118] reported that the incidence rates for the year 1943 were in excess of 25 per thousand troops at some air bases. During the peak of the rheumatic fever season one large post in Colorado experienced a rate of rheumatic fever in excess of 100 per 1,000 men annually. If the subclinical attacks of rheumatic fever, as evidenced by changes in sedimentation rate or electrocardiograms, are included, the rates may be still higher.[209,271]

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How the constitutional predisposition noted in usual civilian practice is effected is not known. Several possibilities exist which have their analogies in studies on experimental animals and on humans. These include the inheritance of some qualitative or quantitative alteration in the host's ability to cope with infection, a predisposition to allergy and an alteration in the end organ affected, in this instance the host's connective tissue system. Inherited strain differences in degree of resistance to infection have been well studied in guinea pigs[160] as have variations in ability to produce antibodies,[152,264] to become passively sensitized;[285] and to become actively allergic.[28] Rheumatics have generally failed to give a personal or family history of increased incidence of allergies such as hayfever or eczema. A greater frequency of reactions to sulfanilamide[174,251] and to non-specific skin tests[227] has been reported but was not noted in another series[91] and has not been recognized with the use of the newer antibiotic agents (personal observations).

In addition, the host's contribution to the illness has been suggested by various studies on dietary deficiencies, particularly in relation to vitamins A and C and proteins.[43,218] These have not been confirmed, however, and the deficiencies have not been shown to differ from alterations occurring in many acute and chronic febrile illnesses. The disease is extremely variable from case to case, and from time to time in the same case. It is, moreover, difficult to make a quantitative appreciation of dietary habits. Therefore, studies on both these variables, the disease and the diet, are difficult to control and evaluate.

Before leaving the consideration of host factors, it should be noted that clinical rheumatic fever may, in a sense, be a magnification of processes that occur to a lesser degree in many individuals recovering from a streptococcic sore throat. It is difficult to draw the line between clinical rheumatic fever and the cases of pharyngitis which continue to have a low fever, a few transient electrocardiographic changes or a mildly elevated sedimentation rate for longer than the usual period of time. The existence of 28 to 50 per cent of 2,500 cases of rheumatic valvular disease without a history of previous recognized rheumatic fever,[151] emphasizes the inadequacy of any attempted differentiation between the apparently minor changes and the full blown rheumatic syndrome. No adequate history of acute rheumatic fever was found among a similar percentage of women with organic valvular disease at the Boston Lying-In Hospital.[103] Rantz, et al.[209] found that about one-third of 185 men with streptococcal sore throat had electrocardiographic changes, elevated sedimentation rate or some manifestation of "continuing disease." Twenty-one of the 185 had electrocardiographic changes similar to those of acute rheumatic fever but only nine had arthritis and were clearly diagnosed as acute rheumatic fever. Watson, Rothbard and Swift[271] found that of 110 cases of scarlet fever eight developed frank rheumatic fever, but eleven others had changes which they considered qualitatively, although not quantitatively, to be those of rheumatic fever. With reference to the occurrence of subclinical pathologic phenomena following streptococcic infections, it is of interest to recall Lyttle's studies in fourteen cases of scarlet fever.[162] He found that all the patients developed a sudden explosive increase in urinary red cells, white cells and casts, by Addis count, about two weeks after the onset of scarlet fever although none developed clinical acute nephritis.

THE AGENT

Many features of acute rheumatic fever resemble aspects of infectious disease. Investigators have naturally sought for an infectious agent as the cause of the rheumatic state. Various organisms have been suggested, including viruses, a virus-streptococcus combination, the tubercle bacillus and various kinds of streptococci.

A virus as the etiologic agent was proposed by Aschoff because the typical myo-

cardial lesions suggested to him the reactions to viruses at other sites in the body. However, the early lesions in rheumatic fever involve the extracellular connective tissue and the later infiltration appears to be a secondary phenomenon. In this selectivity for connective tissue and in its intercellular localization, the pathology of rheumatic fever is unlike that of known virus infections.[250] The virus hypothesis gained in popularity for a time when Schlesinger et al.[225] found particles resembling elementary bodies in pericardial fluid. Although these particles were agglutinated by sera from rheumatic patients, subsequent work by Eagles and Bradley[63] showed that such particles were nonspecifically agglutinated by sera from various types of arthritis, including gonococcal. Attempts to transmit the "virus-like bodies" to monkeys were unsuccessful.[64] In 1945 MacNeal et al. claimed to have transmitted a virus from the blood and pericardial fluid of rheumatics to animals and chick embryos.[168]

In animals, various viruses, pleuropneumonia-like organisms and other agents have been found to cause myocarditis but no association with clinical rheumatic fever could be established.[153,200,222,246]

The demonstration that a streptococcus could not effectively establish itself when instilled onto the nasal mucosa of ferrets unless an influenza virus infection was present[5] is of interest in view of the suggested symbiotic virus-streptococcus relationship in rheumatic fever. However, attacks of influenza and common cold unaccompanied by streptococcal infection have not given rise to rheumatic fever while epidemics of streptococcic tonsillitis, apparently unassociated with virus infection, have resulted in appreciable attacks of rheumatic fever.[36,51,93,213]

It has been stated that the tubercle bacillus is the causative agent of rheumatic fever, particularly in the European literature.[154] While the work on which this hypothesis is based has not been reproducible, it is nevertheless of interest in this discussion because tuberculosis and allergy to the tubercle bacillus have frequently been used as patterns for hypothesis and investigation of the role of the streptococcus or other agents in rheumatic fever. Tuberculin reactions can be produced in various visceral sites in tuberculous animals. The resulting lesions are similar to the nonspecific cellular infiltration that occurs in the various attempts at the experimental production of rheumatic fever. The occurrence of Aschoff-like bodies in tuberculous hearts has been reported.[110,178]

There is now overwhelming evidence that most cases of rheumatic fever can be related to a preceding infection with a hemolytic streptococcus. Acceptance of this relationship has been slow but it is now widespread.

In 1880 Heberden described rheumatic fever and noted that it usually followed acute tonsillitis. In the same year Fowler reported twenty cases of acute rheumatism preceded by tonsillitis. Five years later Mantle reemphasized this relationship and spoke of rheumatic fever as a common complication of infectious sore throat.[93] It remained for Chaedle to present in 1889 the vagaries of clinical rheumatic fever in his classic monograph.[27]

With the application of bacteriologic technics the streptococcus was found to be the most prominent organism in the pharyngeal flora preceding the rheumatic attack. Investigators were first interested chiefly in the Streptococcus viridans and a nonhemolytic streptococcus.[11,205,241,247,276] After attention had been focused on the Streptococcus hemolyticus in scarlet fever,[60] and an antigenic classification of the streptococcus became possible,[147] three reports appeared in England and in the United States which incriminated the hemolytic streptococcus, particularly of Lancefield's group A.[36,51,224] Coburn presented impressive epidemiologic, bacteriologic and immunologic evidence relating the Str. hemolyticus to the infectious process which precedes the development of most of the cases of rheumatic fever.[36,44,45] Since that

time a voluminous literature of confirmatory reports has accumulated.

Bacteriologic and epidemiologic studies have been made of numerous epidemics of sore throat followed by an appreciable incidence of rheumatic fever.[18,44,59,93,207,259,271] The seasonal incidence of hemolytic streptococcus infection has been found to parallel the incidence of rheumatic fever. Coburn[36] cites many references to show the geographic coincidence of the two diseases but this relationship is not as constant as the seasonal incidence. In 1935 Seegal, Seegal and Jost reported that the incidence of acute glomerulonephritis was similar in northern and southern latitudes but that the incidence of hospital admissions for rheumatic fever and scarlet fever was lower in the South.[236] These discrepancies have been resolved somewhat by recent evidence that rheumatic stigmata are rather commonly found at autopsy in tropical countries, and that clinically the disease appears to be much less dramatic in its symptomatology. In addition there is a reported increase in the incidence of rheumatic fever at autopsy in certain tropical countries.[80,105,109,203,277] Rheumatic fever seems to be appreciably frequent in North Africa.[13]

Many cases of rheumatic fever (about 70 per cent in the early studies of Poynton) present themselves with no history of a preceding sore throat. The existence of a subclinical streptococcal infection can frequently be detected by the demonstration of antibodies to many of the antigens of the streptococcus. One of the most widely employed of these is the antibody to the streptococcus hemolysin "O," defined as a serologically distinct entity by Todd.[261] About 80 to 90 per cent of rheumatics studied in many different countries show a rise in the antistreptolysin (ASL) titer.[44,45,94,133,191,207,256,263,282] At first a pathognomonic type of curve with a delayed rise was thought to occur in rheumatic subjects but more recent studies have shown no consistent type of curve. Moreover, a slowly rising curve was found to occur in many other streptococcal infections in which the antigen is found to persist, as in otitis media and other subacute and persistent infections.[96,146,191,256,282]

Antibodies to other antigens derived from the Str. hemolyticus have also been found in acute rheumatic fever. The antifibrinolysin, or antistreptokinase of Christensen and MacLeod,[31] has been studied extensively as evidence of previous infection with hemolytic streptococci in rheumatic individuals.[4,16,100,192,260,282] In addition, skin sensitivity, precipitins and complement-fixing antibodies have been found to "nucleoprotein" fractions of the streptococcus, although with increasing age a fair percentage of normal individuals also show skin sensitivity to these fractions.[11,36,91,106,134,169,232,253] Skin sensitivity and precipitins to the type specific "M" substance have also been described.[48,248,255] None of these antibody responses appears to differentiate the rheumatic from other individuals with infections due to the Str. hemolyticus. It has been reported that the antibody response to the "S" hemolysin is less marked in rheumatics[263] although the differences were not striking. The extreme lability of the substances involved in this reaction makes extensive study difficult. Rantz and Randall[208] reported the increased frequency of an "anti-x" antibody in post-streptococcal arthritis as compared with other post-streptococcal conditions. As yet there has been no adequate definition of the nature of the reported antigen to permit critical comment.

Finally, evidence relating the Str. hemolyticus to the development of rheumatic fever is obtained from the prophylactic use of antibiotics such as the sulfa drugs[41,145,257] and penicillin.[172] The administration of sulfadiazine to naval trainees was accompanied by a diminution of 85 per cent in the incidence of acute tonsillitis and of rheumatic fever when compared to the incidence in control groups.[38] With the appearance of sulfa-resistant strains in some localities tonsillitis and rheumatic fever recurred, exhibiting their usual relationship to each other.

No particular strain or type of group A streptococcus has been shown to have the exclusive property of initiating a rheumatic attack.[220a] The admirable epidemiologic studies of the Army Air Forces Rheumatic Fever Control Program revealed that infection with various types was associated with the subsequent development of rheumatic fever.[125] Indeed it has been suggested that rheumatic fever may be caused by infection with one type, followed by a subsequent infection with another type of hemolytic streptococcus.[125,207] In several epidemics of streptococcus sore throat it was found that the incidence of rheumatic recrudescences was 40 to 60 per cent with all types encountered except Type 4. Infection with the Type 4 streptococcus was followed by no attacks of rheumatic activity in these epidemics.[146] Organisms of this type were found to lack capsular material. One substance known to be present in the capsule is the mucopolysaccharide, hyaluronic acid.[183] It is peculiar that this substance, although widely distributed in the connective tissue and related mesenchymal structures of animals, is present in only one bacterium, the mucoid phase of the Str. hemolyticus of all types except 4 and 22. As yet, many attempts to detect antigenicity in hyaluronic acid have been futile.[52,74,122,137,229]

Despite the mass of evidence linking the hemolytic streptococcus to the rheumatic process, the latter cannot be visualized merely as a kind of infection with the streptococcus but appears to involve other determining mechanisms. That the streptococcal infection *per se* does not constitute the rheumatic process is apparent from the following observations: (1) In rheumatic conditions the joint fluids and blood stream are usually sterile.[286] (2) The frequency of infection with Str. hemolyticus is not paralleled by a similar frequency of rheumatic fever. (3) The severity of the streptococcal infection bears no relation to the severity of the subsequent attack of rheumatic fever. Treatment of the streptococcal infection once it is established has little apparent effect on the development of the subsequent rheumatic attack. (4) In almost all series of rheumatic fever cases there is a small percentage with no history or laboratory evidence of a preceding streptococcal infection. In addition, recrudescences have been observed following various types of trauma,[126] splenectomy[46,132] and typhoid innoculations.[14] Suggestive lesions occur in humans with other infections.[110,178] (5) Streptococcal infection alone cannot constitute the rheumatic process because such infection occurring in known rheumatic subjects is *not* followed by a recrudescence of activity in as many as 50 to 60 per cent of the cases.[42,146] (6) Finally, the lack of chronologic coincidence of the two processes speaks against the identity of rheumatic fever and the infectious process. The latent period between the occurrence of acute tonsillitis and the onset of rheumatic fever was first noted by Haig-Brown in 1899.[51] "An attack of acute rheumatism is very frequently preceded by one of acute tonsillitis; it may be as long a time as five or six weeks but more usually ten days to a fortnight, while as has been already stated, the two may be coincident in time. In fact, it is rare to meet a case of rheumatic fever which has not been recently preceded by a sore throat." It is for these reasons among others that attention was directed away from the infectious process alone and toward the allergic process resulting from it, as the possible cause of rheumatic fever.

THE REACTION

Many observers have suggested that rheumatic fever may be the result of an allergic mechanism. Menzer in 1902 suggested that rheumatic fever displayed certain unusual manifestations which could not be ascribed simply to an infectious process. He is credited with being the first to advance the theory of an allergic type of mechanism at a time when allergy was scarcely defined. Because rheumatic fever resembles the clinical picture of serum sickness, a disease which was the subject of a classic monograph by von Pirquet and Schick,[204] Weintraud[275] believed that an allergic process

was common to both diseases. In the same year (1912) Escherich and Schick suggested an allergic mechanism after observing that the latent period for the development of rheumatic fever following scarlet fever was similar to that period necessary for the production of active sensitization or immunization.[69] In 1914 Herry produced lesions similar to Aschoff nodules by repeated local and intravenous injections into rabbits with an "endotoxin of diplococci" obtained from cases of rheumatic fever. On this basis he subscribed to the allergic hypothesis. His illustrations are rather impressive.[116] He states that his experiments "me paraissent éclairer singulierement la pathogenie de l'arthrite rhumatismale; elles permettent de l'envisage d'une facon toute nouvelle, grâce a la theorie de l'anaphylaxie. Pour moi, l'arthrite rheumatismale serait un phênomène d'anaphylaxie locale."

The experimental study of certain allergic reactions has led many investigators to conclude that an analogous process may result in the tissue damage which is clinically manifested as the rheumatic state. These investigators include Zinsser,[286] Swift,[244,245] Klinge[141] and more recently Brun,[21] Rich[214] and others.

Too often the term "allergy" brings to mind clinical diseases such as hayfever and urticaria. These transient manifestations of the union of certain antigens with their antibodies should be distinguished from the necrotizing types of allergic reactions of which the chief prototypes are the Arthus reaction and the tuberculin reaction.[88,286] Because these reactions cause tissue damage and subsequent cellular infiltration not unlike that which occurs in some rheumatic lesions, it was believed of particular interest that the mechanisms of these be elucidated. In the absence of a method for experimentally inducing rheumatic fever, these reactions provide an hypothetic analog of the rheumatic state. It would be of interest to consider in detail the Arthus reaction, bacterial allergy and a third type of reaction, isosensitization.

The Arthus Reaction and Serum Sickness. The Arthus reaction is a localized necrotic inflammatory response to the union of certain antigens with antibody. It is similar in many respects to anaphylaxis and has unfortunately been called local anaphylaxis with no little confusion of terminology. In each reaction circulating antibody is demonstrable and bears a distinct relationship to the production of the particular lesions. The quantitative relationships of the two reactions have been reviewed by Kabat.[129] Anaphylaxis is in part mediated by histamine or some similar substance, presumably released from cells in the presence of the antigen-antibody complex.[264] The end organ in anaphylaxis is smooth muscle, particularly in one or another locale according to the species of animal studied.[230] In the rabbit the Arthus reaction appears to affect the smooth muscle of the blood vessels.[1] The Arthus reaction, originally produced in the skin, is a more intense and persistent process of an inflammatory nature. By the use of a single protein antigen and known amounts of the homologous antibody, as determined by the quantitative precipitin technic of Heidelberger and Kendall, it has been demonstrated that the severity of the Arthus lesion appears to be directly related to the amount of antibody available to the site of injected antigen.[75] The Arthus reaction has been most widely studied in the skin but it reflects the union of antigen with antibody at any site in the body. Friedberger[83] was the first to produce an aseptic arthritis by the intra-articular injection of a foreign protein, horse serum, into sensitized rabbits. Since then the Arthus type of reaction has been produced experimentally in many sites, including heart and pericardial sac,[9,156,235] joints,[21,140] brain,[53] kidney,[155] eye,[234] lungs,[24,82,97] liver,[108,155] isolated blood vessels[184] and even the vermiform appendix.[78] Other studies of local hypersensitivity in different sites have been reviewed by Seegal, Seegal and Jost.[235]

Clinically the Arthus reaction has its parallel in serum sickness in which residual antigen is known to unite with antibody throughout the body.[127,157,158,170,204] Clark

and Kaplan demonstrated mesenchymal alterations occurring in serum disease in man.[32] Generally the lesions were not as dramatic as those found in experimental work. Besides the local Arthus reactions mentioned above, numerous studies have been made of the systemic or serum sickness type of reaction after injections of foreign proteins into animals. In 1917 Boughton injected guinea pigs with egg white or beef serum repeatedly and found degenerative lesions in all of the livers and spleens and in two-thirds of the kidneys and hearts.[17] Klinge and his school have published extensively on this type of experimental procedure, particularly in Virchow's Archiv 1929–1939. The "hyperergic reaction" is a supposed "morphological equivalent" of rheumatic lesions.[220] The list of other workers who have employed the serum sickness type of technic locally and systemically includes Vaubel,[267] Roessle,[220] Brun[21] and Rich.[214] Of particular interest is the work of Hawn and Janeway.[111] These investigators injected different fractions of plasma proteins—crystalline bovine albumin and highly purified gamma globulin—into rabbits. The former substance resulted in periarteritis-like lesions while the globulin gave predominantly renal lesions. The temporal relationships also differed in the development of these lesions, much as they did in the work of Doerr and Berger.[230] Serologic reactions appear to have a specificity not only *in vitro*[148] but, to a certain degree, *in vivo*.

Bacterial Allergy and Tissue-fixed Antibodies. The tuberculin reaction is the prototype for the bacterial allergic reaction.[88,284,286] It is not transferable with serum of the sensitized animal nor can precipitins be demonstrated in the serum. Rather, it appears that the sensitizing agent, an antibody in the true sense of the word, is fixed to cells of the host. Washed cells from a peritoneal exudate can transfer the sensitivity[29] and in this respect it is similar to the allergy to simple chemical compounds.[149,238] Sensitive white cells are lysed by exposure to the antigen[71] and the growth of connective tissue or bone marrow cell cultures can be inhibited by exposure to the specific antigen.[6,217] Cell cultures from an animal sensitive to horse serum and tuberculin were affected only by the latter.[6] The specificity of the reaction has been corroborated.[188] Similarly the cells of animals sensitive to a "nucleoprotein" extract of streptococci were found to be inhibited by exposure to this antigen.[187] Lurie's work[161] in this connection is particularly pertinent. Mononuclear cells from rabbits immunized to tuberculous infection preserved their power to inhibit the growth of tubercle bacilli when transplanted to the anterior chambers of normal rabbit eyes. Similar cells from normal rabbits did not possess or acquire this property, even when placed in the anterior chamber of the eye of an "immunized" animal or suspended in the serum of such an animal.

The lesions produced in the Arthus and tuberculin reactions are the subject of some discussion. Opie described multiple small thromboses as the basic lesion in the Arthus reaction which then cause cell death secondarily and subsequent polymorphonuclear leukocytic infiltration.[196] This is in accord with Gerlach's observation that the Arthus reaction is not dependent on the leukocytic infiltration but can occur in agranulocytosis.[90] The tuberculin reaction has been described by Dienes and Mallory as chiefly mononuclear in character, even early in the development of the lesion.[57] This was confirmed by Lurie[161] and by Feldman and Fitch,[72] but Rich and Follis[215] found that polymorphonuclear cells predominated. Sabin[223] has shown very impressively that different cellular infiltrations result when various fractions of the tubercle bacillus are injected into sensitized animals. It would appear that the reaction depends on the chemical constitution and toxicity of the antigens employed, the amount of antigen and antibody uniting, the speed of the reaction and the site at which it occurs. These observations again emphasize an aspect of the specificity of immunologic reactions *in vivo*.

Not only can the antibody of the tuber-

culin reaction be demonstrated on the cells of the host but the cells of the inflammatory reaction appear to be responsible in great part for the production of this particular type of allergic reaction. Antigens which ordinarily produce circulating antibody and an edematous wheal and erythema type of response are said to have elicited a tuberculin type of response.[58,104] If egg albumin is injected into a tuberculous focus, the subsequent injection of egg albumin does not elicit the same type of reaction as is induced in animals sensitized to egg albumin according to the usual technic. Rather a delayed reaction results, similar to the tuberculin or severe Arthus reactions. The production of an increased amount of antibody to egg albumin injected into a tuberculous site may account, in part, for the stronger reaction.[75,81] The route of sensitization is known to affect the type of allergic response, the potency of the antigenic stimulus and the type of antibody produced. Thus the intravenous administration of antigens was found to result in an immune type of skin reaction to the antigen, while subcutaneous administration resulted in an allergic inflammatory skin test.[15] The C substance of the streptococcus is an effective antigen when introduced intravenously but not subcutaneously.[233] Using rabbit globulin, Treffers, Heidelberger and Freund[251] showed that intravenous administration in the horse resulted in a characteristic precipitable antibody. The subcutaneous administration of the same antigen gave rise to low grade "univalent" antibody which did not precipitate with the soluble antigen.

These studies are in accord with the view that antibodies are not produced by any single cell type but may be elaborated by almost any cell exposed to the proper stimulus. Local tissue immunity has been the subject of many investigations.[87] Many cells, including the highly specialized cells of the central nervous system[120,130,190] the skin epithelium[56] and mucous membranes[269] have been thought to retain certain basic mechanisms such as sensitization to previously encountered noxious stimuli. Antibody has been clearly demonstrated in corneal tissues sensitized locally when no circulating antibody was demonstrable.[258] It should be emphasized that all these cells need not contribute to the circulating antibody. The latter may well originate from certain cell types,[23] particularly the cells of the reticuloendothelial system[88,89] plasma cells,[12] and perhaps other cells in the lymph nodes.[61,66,167] Such cells appear to have potentialities to become various cell types of mesodermal origin. The inflammatory cells of the classical rheumatic lesion, the Aschoff nodule, may belong to this cytologic family.[33,98,165,166]

The tuberculin reaction has served as a pattern for attempts at the experimental production of rheumatic fever. When living organisms are injected, it is not unlikely that the resulting disturbance may in part be due to an allergic reaction; however, the damage done by the living organism and its toxins frequently confuses the picture. It is therefore easier to evaluate lesions in which only the sterile products of organisms or killed organismsare employed. Magrassi[171] reported that the repeated injection of dead streptococci gave lesions highly suggestive of rheumatic fever. Subsequently, it is stated that some of his lesions may have been due to septicemia.[210] Faber[70] in 1915 and later Hitchcock, Camero and Swift[117] used repeated injections of living and dead streptococci, as did Clawson,[35] and obtained some perivascular and granulomatous lesions. Recently Swift[245a] showed that repeated intradermal infections of rabbits with hemolytic streptococci occasionally resulted in striking cardiac lesions. A pathway for the experimental production of rheumatic fever is indicated by this type of study if it were demonstrated that non-viable fractions of the streptococcus could produce such lesions, and that infections with other organisms did not result in this type of reaction. When tubercle bacilli were injected into the peritonsillar region of rabbits and the animals subsequently injected intravenously with the organisms, lesions of a rheumatic nature were also reported.[3] Products of the strepto-

coccus and other organisms have been used for the production of visceral and vascular lesions of allergy.[116,287] After an extensive review and original work, Gross, Loewe and Eliasoph concluded that lesions produced by this type of technic are not characteristic rheumatic lesions.[99]

Both the Arthus and tuberculin types of reaction have been employed as basic patterns for attempts at the experimental production of rheumatic fever. While these studies are not conclusive and have been challenged,[7] they are highly suggestive. They demonstrate that allergic reactions of the necrotizing variety can be produced in this way and that in certain instances and certain sites particular cells may be intimately sensitized without evidence of such sensitivity in the serum, as in the tuberculin reaction. The pattern for the suggested pathogenesis of rheumatic fever thus has a foundation in the basic mechanisms of these allergic reactions.

Isosensitization and Autosensitization. Other technics have been employed in the study of the pathogenesis of rheumatic fever. The Arthus technic classically employs a foreign antigen and the host's antibody, and the reaction may occur on any tissue surface, with damage to the cells of that vicinity. When the surface itself is made the antigen, a more selective lesion may obtain. The studies of Masugi,[177] Smadel and Farr[240] and Seegal and Loeb[231] on nephrotoxic nephritis basically employ the host's tissue (kidney or placenta) as antigen and use a heterologous antibody. Attempts to do the same, using heart or connective tissue as antigen, have proved less fruitful.[10,52,74] One of the constituents of connective tissue is the mucopolysaccharide hyaluronic acid.[183] Unsuccessful attempts have been made to detect antibodies to this substance. It has been suggested that the failure of hyaluronic acid to function as an antigen or hapten might be accounted for by the fact that the substance occurs normally throughout the mammalian organism.[52,74,122,137,229]

Finally, attempts have been made to employ antigen and antibody derived from the same species—the autoantibody system. In 1933 Burky found that rabbits sensitized to staphylococci also developed sensitivity to the muscle tissue of the broth in which the staphylococci were grown.[22] The observation was extended and it was found that staphylococcal toxin exerted a type of adjuvant, or synergistic effect, which conferred a greater power of antigenicity to rabbit muscle, lens and uveal tissue in rabbits.[159] The observation that rabbits do have a circulating autoantibody[138] has been attributed to the fact that only the older rabbits displayed these antibodies, and they presumably had had infections which may have produced the phenomenon naturally.[128] Generally the streptococcus has not been as potent an adjuvant as the staphylococcus.[228,252] However, Cavelti reported that dead streptococci mixed with rat kidney produced autoantibodies and renal lesions similar to glomerulonephritis in rats. His report on the parallel technic for the production of autoantibodies to rat heart[26] does not have as dramatic illustrations as those of renal lesions. In our experience the results of this type of experiment are inconstant. The most frequent lesions encountered were granulomas of the lung.[74] These and other abnormalities occurred with Freund's emulsion and tubercle bacilli alone. Recently, Peck and Thomas reported the failure to produce rheumatic-like lesions using tissue extracts, streptococci and adjuvants.[201] The analogous experiment with homologous brain tissue and the adjuvants of Freund and McDermott[81] produces striking lesions in the central nervous system of monkeys.[131,189]

Clinically, isoantibodies do frequently cause damage to humans in such situations as erythroblastosis fetalis, the Donath-Landsteiner phenomenon, acquired hemolytic icterus and occasionally cold agglutination. However, the commonly observed Wassermann antibody in syphilis is an antibody to a constituent of normal tissues[54,85,274] and does not appear to produce widespread tissue damage, nor does the naturally occurring antibody to rabbit tis-

sues appear to be a detrimental influence to the rabbit.[138]

Lack of Specificity of the Pathology of Necrotizing Allergies. The criteria for the establishment of the relationship of allergy to certain infectious diseases have been discussed by Opie.[197] Substantial difficulties are present in any attempt to ascribe an allergic basis for the manifestations of readily diagnosable infectious diseases. In the consideration of rheumatic fever these difficulties are increased by the additional uncertainty attendant upon the clinical definition of the rheumatic state. Reports of the experimental production of rheumatic fever have met with several cogent criticisms. Unfortunately, the diagnosis of rheumatic fever clinically does not involve any single pathognomonic finding. In animals the criteria for the production of the rheumatic state are even more confusing and usually rest on the lesions produced. Again and again it becomes necessary to recall the axiom that the body can react in but a limited number of ways to numerous and varied stimuli. Viruses may cause cell proliferation or cell death, with attendant secondary effects on blood supply and cellular infiltration. Various other infectious agents, neoplasms and physical stimuli can cause similar pictures. Many chronic infections and some acute ones present the well known perivascular accumulation of lymphocytes and mononuclear cells. Experimentally and clinically, this has been seen with all types of pyogenic bacteria, acid-fast bacilli, viruses, etc.[2,19,79,144,173,194,239,266] Oeller[195] showed that perivascular accumulation of mononuclear cells occurred within an hour after injection of avian erythrocytes into guinea pigs. In acute reactions the perivascular and intravascular lesions resemble those of periarteritis nodosa.[143,182,216] Such lesions have been found in a variety of conditions such as asthma,[279] gonococcal septicemia[114] and sulfa sensitivity.[214]

This lack of versatility on the part of the body in reacting to many injuries is emphasized by students of Klinge and more recently by Klemperer[139] and Selye.[237] The criteria for the establishment of an allergic process as the cause of a disease cannot, therefore, be as specific as the criteria postulated by Koch for the determination of the etiologic agent in infectious disease.[197] However, within limits, there does appear to be a certain specificity of immunologic reactions *in vivo*, as was noted previously.

Rheumatic fever has been diagnosed by a number of morphologic changes:[92,164] (1) There is, at first, swelling and "fibrinoid" degeneration in the ground substance surrounding the connective tissue fibrils.[140,141,254] (2) The site of the reaction is chiefly in the connective tissue, usually in the septa of the heart and around blood vessels although there is adequate clinical and pathologic evidence that the disease is widespread throughout the body.[142,164,198] (3) Round cell infiltration of a non-specific nature occurs, as discussed above, along with proliferation and hyperplasia of the connective tissue cells and the appearance of "specific" Aschoff cells. These latter cells may be a type of plasma cell or a derivative of the cardiac connective tissue cell.[7,8,67,98,165,243] The specificity of these cells, so strongly maintained by Aschoff,[7] is open to question. (4) Finally, hyalinization and scar formation occurs in the collagenous septa or in the connective tissue of the cardiac valves.

The sequence of these lesions has been debated[50] but each or all of them are used by experimental workers as criteria for "rheumatic" activity. However, these lesions can be produced singly or in combination by various stimuli: physical (pinching the skin[283]), chemical (allyl amine,[68] benzpyrene,[150] nitrites[121]), hormonal (adrenal hormones,[202,237] thyroxin,[181] pitressin,[193]), and other stimuli.[139] Various infections, as previously stated, and in addition "malignant" hypertension,[30,237] scurvy[163,219,226] and other severe systemic illnesses give rise to some of these lesions. Indeed, these stigmata may be quite common, for Hall and Anderson report that rheumatic stigmata were found in about 90 per cent of 112 hearts

studied minutely although none showed evidence clinically or grossly of rheumatic fever.[102] "Spontaneous" cardiovascular lesions occur frequently in rabbits and rats[185,278] and are probably the result of naturally occurring infections. Chronic valvular disease, similar to that produced clinically by rheumatic fever, has not been produced by the experimental procedures discussed above. This lesion has been obtained only after the use of living organisms, which presumably cause an acute septic endocarditis and then a healed or chronically infected scarred valvulitis.[35]

Subcutaneous nodules and erythema nodosum are other lesions which have been studied in an attempt to elucidate the mechanism of production of the rheumatic state. Here again there is a lack of specific histologic character and a variety of clinical and experimental conditions associated with the appearance of these lesions.[135] These preclude a definitive statement concerning the specific role of the experimental procedures said to induce the lesions. Trauma and the subcutaneous injection of the patient's own blood have been employed to induce the formation of subcutaneous nodules[175] but another investigator failed to repeat this observation.[107] Injections of a proteolytic enzyme have also been reported to stimulate the formation of subcutaneous nodules.[186] Subsiding erythema nodosum was reactivated in tuberculous patients by the injection of old tuberculin.[40] A similar phenomenon has been observed in rheumatic subjects injected with streptococcal nucleoprotein.[40]

CLINICAL STUDIES CONCERNING THE ALLERGIC MECHANISM IN RHEUMATIC FEVER

The evidence that an allergic type of mechanism may produce the rheumatic process is strongly suggestive but, as yet, only suggestive. It is based chiefly on the clinical aspects suggesting allergy (latent period, etc.) previously cited and the morphologic analogy between rheumatic lesions and those produced by necrotizing allergic reactions in experimental animals. Clinical studies of rheumatic patients have usually served to substantiate the occurrence of a preceding streptococcal infection by documenting the appearance of circulating antibodies or skin sensitivity in rheumatic patients. However, these responses do not appear to differ qualitatively or quantitatively from those of normal individuals with streptococcal infections, particularly if the infection is persistent. To determine the antigens or antibodies involved in the presumed allergic reaction would serve to establish a pathognomonic basis for the allergic hypothesis. There are relatively few reports on work of this type. These are chiefly concerned with attempts to demonstrate antibodies in rheumatic patients not found in other individuals recovering from streptococcal infections.

The Phase Reaction. In 1939 Coburn and Pauli reported that following a sore throat in a rheumatic subject a substance called a "precipitinogen" appears in the serum and precipitates with a component of the serum taken during the subsequent rheumatic attack.[49] Because the reaction appeared to occur when serum taken during phases I and II (the sore throat and the latent periods) was mixed with serum from phase III (the period of rheumatic activity), it has been called the "phase reaction." Wedum and Wedum confirmed some of these observations but found a greater degree of nonspecificity for the reaction and a different time relationship for the appearance of the presumed antigen and antibody.[273] This phenomenon was further studied with various control tests[77] and was found to be non-specific and irregularly reproducible. Further, it appears that when precipitation does occur it does not present the characteristics of the usual precipitin test nor lend itself to passive transfer, dilution or complement fixation tests. It cannot, therefore, be considered an antigen-antibody reaction.

Autoantibodies in Rheumatic Fever. Other clinical findings suggesting an allergic mechanism in rheumatic fever have been reported. The concept of an autoantibody in rheumatic fever was suggested by Brok-

man, Brill and Frendzel.[20] These investigators found that sera from rheumatic patients fixed complement when mixed with an extract of liver obtained at the autopsy of a rheumatic individual. Sera from other diseases did not fix complement with this "antigen." Unfortunately, anticomplementary controls were not reported. It is well known that tissue extracts are frequently anticomplementary, as are, occasionally, rheumatic and other sera in certain concentrations. Complement fixation is reported to occur with liver tissue and the sera from some normal individuals as well as those with a variety of illnesses.[65] In our experience[77] no evidence of complement fixation was found in dilutions of rheumatic serum and of tissue extracts that were not anticomplementary alone. If complement fixation occurred, it would be difficult to distinguish the reaction from a non-specific false positive Wassermann type of reaction. The same criticism applies to many attempts to demonstrate autoantibody reactions with tissue extracts. Cavelti[25] employed the collodion particle technic to detect agglutination of antigen by antibody. One of four normal (i.e., non-rheumatic) hearts used as antigen reacted strongly with sera from twenty-seven of thirty-six rheumatic patients studied. Subsequently Cavelti could not reproduce the phenomenon with other heart preparations (personal communication).

Using the technic of Cavelti it has been observed that collodion particles coated with various tissue extracts, particularly from lung, kidney and tonsil, were agglutinated by a few rheumatic sera but more regularly by syphilitic sera.[77] Therefore, the possibility continues that the reaction noted is similar to a biologically false positive flocculation test for syphilis. It is of interest that the Wassermann antigen is a constituent of normal tissue.[54,274] The occurrence of biologically false positive Wassermann reactions in many diseases has been reviewed by Davis.[54] Another possible explanation of the positive reactions is that bacterial contamination of the tissues used may serve as antigens for antibodies in the sera. Thus, collodion particles mixed with an extract of tonsillar tissue were regularly agglutinated by some sera as might be anticipated since the tonsils had been infected with hemolytic streptococci.[77]

Serum Complement in Rheumatic Fever. The fixation of complement by many antigen-antibody aggregates in the test tube (phenomenon of Bordet and Gengou[88]) suggested a third experimental approach to the documentation of an allergic process in rheumatic fever. Serum complement, normally maintained with little variation, has been observed to fall in anaphylactic shock[84] when sheep cells and amboceptor are injected into guinea pigs[123] and in serum sickness.[221]

In the study of rheumatic fever there has been disagreement and confusion as to the activity of serum complement. Veil and Buccholtz,[268] Coburn,[37] Rachmilewitz and Silberstein[206] and others have reported a low complement content of the serum in some cases of rheumatic fever, which rises to normal with subsidence of activity. This has been cited as evidence of the occurrence of an antigen-antibody reaction in rheumatic fever. There are several causes for a low serum complement other than fixation by antigen-antibody aggregates. Decreased production of complement is said to occur in liver disease and perhaps in many terminal illnesses. Also, complement levels may be diminished by the presence of inhibitory or anticomplementary substances in the serum. Anticomplementary sera are occasionally found in routine Wassermann tests. The nature of the substances responsible for the inhibition or inactivation of complement is not clear. One such substance may be gamma globulin, a relative preponderance of which causes serum to become anticomplementary.[55]

Predominantly normal or slightly low levels of complement in rheumatic fever were reported by Kellett and Thompson[136] and more recently by de Gara and Goldberg.[86] On the other hand, high values during the early period of rheumatic activity were noted by Hadjapoulos and

Burbank in 1928.[101] In this respect rheumatic fever did not differ from other febrile illnesses which they studied. The variety of results obtained by different investigators may be attributed in part to the variety of technics employed and the lack until recently of a reproducible quantitative method for the determination of complement. A satisfactory and reproducible method was described by Mayer, Osler, Bier and Heidelberger in 1946.[179] The 50 per cent hemolytic unit of complement is determined spectrophotometrically in the presence of optimal quantities of magnesium and calcium. Employing this technic fifty cases of active rheumatic fever were studied serially.[77] Only two showed an initial depression of serum complement, which gradually became normal. In the remaining cases elevated complement levels were found similar to the elevated complement content of sera from various illnesses including pneumonias and penicillin sensitivity. Since there is an elevation of complement in certain allergies studied, the high complement content of most of the rheumatic sera does not preclude the possibility that rheumatic fever may also be an allergic reaction. However, the presence of an elevated complement level in these sera contradicts the suggestion that the low levels previously reported are experimental evidence of an allergic process.

ATTEMPTS TO ALTER THE REACTION

"Specific" Measures. Specific desensitization or immunization of the host to an offending antigen would make more acceptable the hypothesis that rheumatic fever is the result of an allergic process. However, it is difficult if not impossible to desensitize or immunize to bacterial allergic reactions[148,230,264] and, in instances in which this has been achieved, periods of non-reactivity to injected antigens are only temporary. Furthermore, non-reactivity of the skin may depend on non-specific factors such as vascularity while the basic sensitivity of other tissues remains unaltered. Thus, in the presence of a negative skin reaction to tuberculin, explants of splenic tissue culture showed sensitivity to tuberculin.[113] Attempts at specific desensitization or immunization of rheumatic subjects with streptococcal antigens have been reported to be of some benefit[270] but were abandoned after trial by others.[47,249,281] Active immunization, in order to be possible, would obviously depend upon the characteristics of the particular antigen employed.

Unlike the attempts at desensitization or immunization, avoidance of the suspected antigen appears to have been more beneficial. Chemoprophylaxis against the streptococcus, as discussed previously, has become a valuable instrument in the management of rheumatic fever.[41,145,257]

Non-specific Measures. Many agents have been used in the treatment of rheumatic fever but few have remained as constantly in use as have the salicylates and others of the so-called antirheumatic group of drugs. Salicylates have been employed for many years, usually in dosage approaching the limit of tolerance. Despite the popularity of the salicylates and their dramatic effect on fever and arthralgia, their basic efficacy has been questioned.[95,176] In the opinion of many, salicylates do decrease the severity of the disease if administered early and perhaps shorten the course of the illness as well. The mechanism of the action of salicylate has remained obscure despite its widespread use over so long a period of time. Investigators have sought for an action more specific to the rheumatic process than the antipyretic and analgesic properties of salicylates. In relation to immunity, salicylates have been said to impair antibody production.[119,242] However, the differences reported were not striking for the technics employed. The formation of antibodies to typhoid vaccine in rheumatic subjects on salicylate therapy was apparently inhibited[124] as compared with the formation of antibodies in normal subjects not on salicylates, a rather unsatisfactory control group. Salicylates caused diminished inflammation at the site of injection of the typhoid vaccine and this

may also account for differences observed, since in certain instances inflammation appears to augment antibody production.[81] Fischel and LeMay (unpublished) immunized four rabbits with crystalline egg albumin intravenously and administered large doses of salicylate three times daily for four to eight weeks. The amount of specific antibody, as determined by the quantitative precipitin technic,[112] was comparable to the amount of antibody in the sera of six animals similarly immunized but not treated with salicylate.

Another hypothesis for the mechanism of action of salicylates that has been suggested is that it interferes with the union of antigen and antibody.[39] In the test tube, less precipitin was found between egg albumin and anti-egg albumin in the presence of salicylate. The extent of this inhibition is slight in relation to the degree of error inherent in the quantitative precipitin technic, and salicylates were employed in approximately ten times maximal concentrations achieved *in vivo*. In animals and in humans there appeared to be no inhibition of allergic reactions of the Arthus and bacterial types by salicylates.[73]

Clinical and experimental data have shown no effect of various antihistamine compounds on rheumatic fever or on experimental necrotizing allergies.[73,74] However, an unusually potent antihistamine, phenergan, possessing other anti-inflammatory properties was found to inhibit the Arthus reaction.[10a]

Recently Hench and his co-workers demonstrated that cortisone or adrenocorticotrophic hormone (ACTH) produces a dramatic defervescence of activity in rheumatoid arthritis and rheumatic fever.[115a] The mechanism of action of these hormones is still obscure but speculation concerning the effect of these hormones on immune mechanisms has been advanced.[206a] Two of several steps in the development of immunity have been studied. ACTH was found to have no influence as an anamnestic stimulus on the production of antibody[76] and did not affect the tissue damage resulting from the union of antigen and antibody *in vivo* in the Arthus and anaphylaxis reactions studied by passive, quantitative methods,[74, 241a] or in anaphylaxis induced after active immunization.[149a] However, the efficacy of these hormones in clinical hay fever and asthma, noted incidentally in the course of treatment of rheumatoid arthritis and other conditions, suggests that an effect on immune mechanisms is present, and that this effect may also be one of the modes of action of these hormones in rheumatic diseases.[206a] The experimental study of this hypothesis should prove intriguing.

SUMMARY

Rheumatic fever occurs in certain predisposed individuals but the incidence in some epidemics, and of subclinical cases, appears to exceed estimates based on genetic studies. There is a definite relationship to a preceding infection with the group A hemolytic streptococcus in the great majority of cases of rheumatic fever adequately studied. However, for many reasons summarized the infection does not appear to play more than an initial role in the rheumatic process; rather, a host reaction or allergy to the infection, as has frequently been suggested, is probably the basis for the development of the disease.

Various kinds of necrotizing allergic reactions are reviewed with reference to the mechanisms initiating them. The Arthus type of reaction is related to a circulating antibody and has its clinical counterpart in serum sickness. It has been used extensively as a pattern for attempts at the experimental production of rheumatic-like lesions. The bacterial allergic reactions are distinguished by having fixed tissue antibodies. They have also been used as patterns for animal experimentation. Other experimental approaches involve the use of isoantibodies (cytotoxic antibodies) and autoantibodies. In the absence of other than morphologic criteria, the specificity of the experimentally induced lesions is not adequately established. They cannot, therefore, be unequivocally identified with the lesions of the rheumatic

state although they suggest by analogy that lesions similar to those seen in rheumatic fever may be induced by various allergens.

Clinical studies are reviewed which attempt to define an allergic process in rheumatic patients. Technics involving the detection of isoprecipitins and autoantibodies do not appear constant or specific in this respect and may reflect the occurrence of biologically false positive Wassermann reactions. In the study of serum complement in rheumatic fever various technics have given variable results. A predominantly high complement level in rheumatic fever was found in a recent study. This does not exclude the occurrence of an allergic reaction of the fixed tissue type because several cases of drug allergy also presented high complement levels. There is, as yet, no clinical test for the detection of an allergic reaction in rheumatic individuals that does not occur in patients recovering from a streptococcal infection or certain other diseases.

Finally certain measures employed in rheumatic fever are reviewed with respect to their effect on antigen-antibody reactions. Specific desensitization with the hemolytic streptococcus has been of doubtful value. Salicylates are usually effective in producing a remission of rheumatic activity. However, they apparently do not act on antibody producing mechanisms or by altering the severity of known allergic reactions. The dramatic effectiveness of cortisone or ACTH in the rheumatic diseases should prove extremely valuable in the future study of the pathogenesis of these diseases. The role of these hormones in immune mechanisms, as well as other processes, has yet to be fully studied.

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REFERENCES

1. Aeell, R. G. and Schenck, H. P. Microscopic observations on the behavior of living blood vessels of the rabbit during the reaction of anaphylaxis *J. Immunol.*, 34: 195, 1938.
2. von Albertini, A. and Grumbach, A. Die experimentelle Streptokokkeninfektion des Kaninchens in ihren Beziehungen zur Herdinfektion. *Ergebn. d. Allg. Path. u. path. Anat.*, 33: 314, 1937.
3. Altmann, F. and Gerzner, L. Über die Bedeutung der Tonsillen, bzw. des peritonsillären Gewebe für das Zustandekommen hyperergisch entzündlicher Gewebsveränderungen auf tuberküloser Basis. *Virchows Arch. f. path. Anat.*, 296: 480, 1935.
4. Anderson, H. C., Kunkel, H. G. and McCarty, M. Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci: a comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever. *J. Clin. Investigation*, 27: 425, 1948.
5. Andrews, C. H. and Glover, R. E. Spread of infection from the respiratory tract of the ferret. I. Transmission of influenza A virus. *Brit. J. Exper. Path.*, 22: 91, 1941.
6. Aronson, J. D. The specific cytotoxic action of tuberculin in tissue culture. *J. Exper. Med.*, 54: 387, 1931.
7. Aschoff, L. The rheumatic nodules in the heart. *Ann. Rheumat. Dis.*, 1: 161, 1939.
8. Aschoff, L. and Tawara, S. Die heutige Lehre von den pathologischanatomischen Grundlagen der Herzschwäche. Jena, 1906. G. Fisher.
9. Baker, B. M., Thomas, C. B. and Penick, R. M., Jr. Experimental carditis. Changes in the myocardium and pericardium of rabbits sensitized to streptococci. *J. Clin. Investigation*, 14: 465, 1935.
10. Bauer, F. C., Jr. Reaction of rats following injection of anti-rat-heart immune serum. *Arch. Path.*, 42: 222, 1946.

10*a*. Benacerraf, B. and Fischel, E. E. Effect of phenergan on the Arthus reaction in rabbits. *Proc. Soc. Exper. Biol. & Med.*, 71: 349, 1949.

11. Birkhaug, K. E. Rheumatic fever: allergic reactions with a toxin-producing strain of non-methemoglobin-forming streptococcus isolated from rheumatic fever. *J. Infect. Dis.*, 43: 280, 1928.
12. Bjørneboe, M., Gormsen, H. and Lundquist, F. Further experimental studies on the role of the plasma cells as antibody producers. *J. Immunol.*, 55: 121, 1947.
13. Bland, E. F. Rheumatic fever and rheumatic heart disease in the North African and Mediterranean Theater of Operations, U.S. Army. *Am. Heart J.*, 32: 545, 1946.
14. Bland, E. F. and Jones, T. D. Clinical observation on the events preceding the appearance of rheumatic fever. *J. Clin. Investigation*, 14: 633, 1935.
15. Böhmig, R. and Swift, H. F. Comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously. *Arch. Path.*, 15: 611, 1933.
16. Boisvert, P. L. The streptococcal antifibrinolysin test in clinical use. *J. Clin. Investigation*, 19: 65, 1940.

17. Boughton, T. H. Vascular lesions in protein intoxication. *J. Immunol.*, 2: 501, 1917.
18. Bradley, W. H. Epidemic acute rheumatism in a public school. *Quart. J. Med.*, 1: 79, 1932.
19. Brody, H. and Smith, L. W. The visceral pathology in scarlet fever and related streptococcus infections. *Am. J. Path.*, 12: 373, 1936.
20. Brokman, H., Brill, J. and Frendzel, J. Komplementablenkung mit Organextrakten von Rheumatikern. *Klin. Wchnschr.*, 16: 502, 1937.
21. Brunn, E. Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatic Joint Diseases. London, 1940. Oxford University Press. Also *Virchow's Arch.*, 303: 524, 1939.
22. Burky, E. L. The production in the rabbit of hypersensitive reactions to lens, rabbit muscle and low ragweed extracts by the action of staphylococcus toxin. *J. Allergy*, 5: 466, 1934.
23. Burnet, F. M. The Production of Antibodies. Melbourne, 1941. Macmillan & Co., Ltd.
24. Cannon, P. R., Walsh, T. E. and Marshall, C. E. Acute local anaphylactic inflammation of the lungs. *Am. J. Path.*, 17: 777, 1941.
25. Cavelti, P. A. Autoantibodies in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 379, 1945.
26. Cavelti, P. A. Studies on the pathogenesis of rheumatic fever. II. Cardiac lesions produced in rats by means of autoantibodies to heart and connective tissue. *Arch. Path.*, 44: 13, 1947.
27. Chaedle, W. B. The Various Manifestations of the Rheumatic State as Exemplified in Childhood and Early Life. London, 1889. Smith, Elder & Co.
28. Chase, M. W. Inheritance in guinea pigs of the susceptibility to skin sensitization with simple chemical compounds. *J. Exper. Med.*, 73: 711, 1941.
29. Chase, M. W. The cellular transfer of cutaneous hypersensitivity to tuberculin. *Proc. Soc. Exper. Biol. & Med.*, 59: 134, 1945.
30. Child, C. G. Observations on the pathological changes following experimental hypertension produced by constriction of the renal artery. *J. Exper. Med.*, 67: 521, 1938.
31. Christensen, L. R. and MacLeod, C. M. Streptococcal fibrinolysis: a proteolytic reaction due to a serum enzyme activated by streptococcal fibrinolysin. *J. Gen. Physiol.*, 28: 559, 1945.
32. Clark, E. and Kaplan, B. I. Endocardial, arterial and other mesenchymal alterations associated with serum disease in man. *Arch. Path.*, 24: 458, 1937.
33. Clawson, B. J. The Aschoff nodule. *Arch. Path.*, 8: 664, 1929.
34. Clawson, B. J. Experimental streptococcic inflammation in normal, immune and hypersensitive animals. *Arch. Path.*, 9: 1141, 1930.
35. Clawson, B. J. Experimental endocarditis (rheumatic-like and bacterial) in rats. *Arch. Path.*, 40: 153, 1945.
36. Coburn, A. F. The Factor of Infection in the Rheumatic State. Baltimore, 1931. Williams and Wilkins.
37. Coburn, A. F. Observations on the mechanism of rheumatic fever. *Lancet*, 2; 1025, 1936.
38. Coburn, A. F. The prevention of respiratory tract bacterial infections. *J. A. M. A.*, 126: 88, 1944.
39. Coburn, A. F. and Kapp, E. M. The effect of salicylates on the precipitation of antigen with antibody. *J. Exper. Med.*, 77: 173, 1943.
40. Coburn, A. F. and Moore, L. V. Experimental induction of erythema nodosum. *J. Clin. Investigation*, 15: 509, 1936.
41. Coburn, A. F. and Moore, L. V. The prophylactic use of sulfanilamide in streptococcal respiratory infections, with especial reference to rheumatic fever. *J. Clin. Investigation*, 18: 147, 1939.
42. Coburn, A. F. and Moore, L. V. Salicylate prophylaxis in rheumatic fever. *J. Pediat.*, 21: 180, 1942.
43. Coburn, A. F. and Moore, L. V. Nutrition as a conditioning factor in the rheumatic state. *Am. J. Dis. Child.*, 65: 744, 1943.
44. Coburn, A. F. and Pauli, R. H. Observations on the immunological responses of rheumatic subjects to hemolytic streptococcus. *J. Exper. Med.*, 56: 651, 1932.
45. Coburn, A. F. and Pauli, R. H. The significance of the rise in antistreptolysin level in the development of rheumatic activity. *J. Clin. Investigation*, 14: 769, 1935.
46. Coburn, A. F. and Pauli, R. H. Splenectomy in relation to the development of rheumatic activity. *J. Clin. Investigation*, 14: 783, 1935.
47. Coburn, A. F. and Pauli, R. H. Active and passive immunization to hemolytic streptococcus in relation to the rheumatic process. *J. Clin. Investigation*, 14: 763, 1935.
48. Coburn, A. F. and Pauli, R. H. The significance of prolonged streptococcal antibody development in rheumatic fever. *J. Clin. Investigation*, 18: 141, 1939.
49. Coburn, A. F. and Pauli, R. H. A precipitinogen in the serum prior to the onset of acute rheumatism. *J. Exper. Med.*, 69: 143, 1939.
50. Collins, D. H. Observations on the pathology of acute rheumatism and rheumatoid arthritis. *Ann. Rheumat. Dis.*, 1: 38, 1939.
51. Collins, W. R. F. Acute rheumatism and hemolytic streptococci. *Lancet*, 1: 1341, 1931.
52. Coss, J. A., Jr. Unpublished.
53. Davidoff, L. M., Seegal, B. C. and Seegal, D. The Arthus phenomenon. Local anaphylactic inflammation in the rabbit brain. *J. Exper. Med.*, 55: 163, 1932.
54. Davis, D. Biologic false positive serologic tests for syphilis. *Medicine*, 23: 359, 1944.
55. Davis, B. D., Kabat, E. A., Harris, A. and Moore, D. H. The anticomplementary activity of serum gamma globulin. *J. Immunol.*, 49: 223, 1944.
56. Dienes, L. The participation of cutaneous epithelium in immunity response. *J. Immunol.*, 24: 253, 1933.
57. Dienes, L. and Mallory, T. B. Histological studies of hypersensitive reactions. *Am. J. Path.*, 8: 689, 1932.
58. Dienes, L. and Schoenheit, E. W. The reproduction of tuberculin hypersensitiveness in guinea pigs with various protein substances. *Am. Rev. Tuberc.*, 20: 92, 1929.

59. Ditkowsky, S. P., Stevenson, E. and Campbell, J. M. An epidemic of rheumatic fever in a children's institution. *J. A. M. A.*, 121: 991, 1943.
60. Dochez, A. R. Etiology of scarlet fever. *Harvey Lect.*, 20: 131, 1924–25.
61. Dougherty, T. F. and White, A. An evaluation of alterations produced in lymphoid tissue by pituitary-adrenal cortical secretion. *J. Lab. & Clin. Med.*, 37: 584, 1947.
62. Draper, G. and Seegal, D. The importance to the clinicians of the study of genetics. Genetic survey of 50 families with acute rheumatic fever. *Eugenical News*, p. 62, July, 1923.
63. Eagles, G. H. and Bradley, W. H. Agglutination of suspensions of virus-like particles prepared from exudates in acute rheumatic fever. *Quart. J. Med.*, 8: 173, 1939.
64. Eagles, G. H., Evans, P. R., Keith, J. D. and Fisher, A. G. T. Infection experiments with virus-like bodies from rheumatism. *J. Path. & Bact.*, 46: 481, 1938.
65. Eaton, M. D., Murphy, W. D. and Hanford, V. L. Heterogenetic antibodies in acute hepatitis. *J. Exper. Med.*, 79: 539, 1944.
66. Ehrich, W. E. and Harris, T. N. Formation of antibodies in the popliteal lymph node in rabbits. *J. Exper. Med.*, 76: 335, 1942.
67. Ehrlich, J. C. and Lapan, B. The Anitschkow "myocyte." *Arch. Path.*, 28: 361, 1939.
68. Eppinger, H., Faltitschek, J., Kaunitz, H. and Popper, H. Über seröse Entzündung. *Klin. Wchnschr.*, 13: 1105, 1137, 1935.
69. Escherich, T. and Schick, B. Der Scharlach. Wien, 1912. Hölder.
70. Faber, H. K. Experimental arthritis in the rabbit; contribution to the pathogeny of arthritis in rheumatic fever. *J. Exper. Med.*, 22: 615, 1915.
71. Favour, C. B. Lytic effect of bacterial products on lymphocytes of tuberculous animals. *Proc. Soc. Exper. Biol. & Med.*, 65: 269, 1947.
72. Feldman, W. H. and Fitch, C. P. Histologic feature of the intradermic reaction to tuberculin in cattle. *Arch. Path.*, 22: 495, 1936.
73. Fischel, E. E. Effect of salicylate and tripelennamine hydrochloride (pyribenzamine) on the Arthus reaction and on bacterial allergic reactions. *Proc. Soc. Exper. Biol. & Med.*, 66: 537, 1947.
74. Fischel, E. E. Unpublished.
75. Fischel, E. E. and Kabat, E. A. A quantitative study of the Arthus phenomenon induced passively in the rabbit. *J. Immunol.*, 55: 337, 1947.
76. Fischel, E. E., LeMay, M. and Kabat, E. A. The effect of adrenocorticotrophic hormone and x-ray on the amount of circulating antibody. *J. Immunol.*, 61: 89, 1949.
77. Fischel, E. E. and Pauli, R. H. Serological studies in rheumatic fever. I. The "phase" reaction and the detection of autoantibodies in the rheumatic state. *J. Exper. Med.*, 89: 669, 1949. II. Serum complement in rheumatic fever. *J. Clin. Investigation*, 28: 1172, 1949.
78. Fischer, E. and Kaiserling, H. Die experimentelle lymphogene allergischhyperergische Appendicitis. *Virchows Arch. f. path. Anat.*, 297: 146, 1936.
79. Fischl, J. Beitraege zur Histologie des Scharlachniere. *Ztschr. f. Heilk.*, 4: 1, 1883.
80. Francisco, R. Rheumatic heart disease in the tropics with special reference to its incidence in Puerto Rico. *Clinics*, 5: 971, 1946.
81. Freund, J. and McDermott, K. Sensitization to horse serum by means of adjuvants. *Proc. Soc. Exper. Biol. & Med.*, 49: 548, 1942.
82. Fried, B. M. Allergic inflammation of the lungs; pathogenesis of lobar pneumonia. *Arch. Path.*, 18: 865, 1934.
83. Friedberger. Über aseptisch erzeugte Gelenkschwellungen beim Kaninchen. *Berl. klin. Wchnschr.*, 50: 88, 1913.
84. Friedberger, E. and Hartoch, O. Über das Verhalten des Komplements bei der aktiven und passiven Anaphylaxie. *Ztschr. f. Immunitätsf.*, 3: 581, 1909.
85. Furth, J. and Kabat, E. A. Association of the Wassermann antigen with heavy material present in tissue. *Science*, 94: 46, 1941.
86. deGara, P. F. and Goldberg, H. P. Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. III. Complement titers in abnormal conditions. *Pediatrics*, 2: 248, 1948.
87. Gay, F. P. Tissue resistance and immunity. *Harvey Lect.*, 26: 162, 1930–31.
88. Gay, F. P. et al. Agents of Disease and Host Resistance. Springfield, 1935. Charles C. Thomas.
89. Gay, F. P. and Clark, A. R. Reticuloendothelial system in relation to antibody formation. *J. A. M. A.*, 83: 1296, 1924.
90. Gerlach. Neue Versuche über hyperergische Entzündung. *Verhandl. d. deutsch. path. Gesellsch.*, 20: 272, 1925.
91. Gibson, H. J., Thomson, W. A. R. and Stewart, D. The hemolytic streptococcus as a factor in the causation of acute rheumatism. *Arch. Dis. Childhood*, 8: 57, 1933.
92. von Glahn, W. C. Pathology of rheumatism. *Am. J. Med.*, 2: 76, 1947.
93. Glover, J. A. and Griffith, F. Acute tonsillitis and some of its sequels: epidemiological an bacteriological observations. *Brit. M. J.*, 2: 521, 1931.
94. Goldie, W. The hemolytic streptococcus in the aetiology of rheumatic fever and rheumatoid arthritis. *Lancet*, 2: 246, 1938.
95. Graef, I., Parent, S., Zitron, W. and Wyckoff, J. Studies in rheumatic fever. I. The natural course of acute manifestations uninfluenced by "specific" therapy. *Am. J. M. Sc.*, 185: 197, 1933.
96. Green, C. A. Observations on antistreptolysin O titer in relation to mechanism of acute rheumatic fever. *J. Path. & Bact.*, 53: 223, 1941.
97. Gregory, J. E. and Rich, A. R. The experimental production of anaphylactic pulmonary lesions with the basic characteristics of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.*, 78: 1, 1946.
98. Gross, L. and Ehrlich, J. C. Studies on the myocardial Aschoff body. *Am. J. Path.*, 10: 467 and 489, 1934.
99. Gross, L., Loewe, L. and Eliasoph, B. Attempts to produce rheumatic fever in animals. *J. Exper. Med.*, 50: 41, 1929.
100. Hadfield, G., Magee, V. and Perry, C. B. The

lysis of fibrin by streptococci: its application to the problems of rheumatic infection in children. *Lancet*, 1: 834, 1934.

101. HADJOPOULOS, L. G. and BURBANK, R. The role of complement in health and disease. A clinical study of the hemolytic complement of human sera. *J. Lab. & Clin. Med.*, 14: 131, 1928.
102. HALL, E. M. and ANDERSON, L. R. The incidence of rheumatic stigmas in hearts which are usually considered non-rheumatic. *Am. Heart J.*, 25: 64, 1943.
103. HAMILTON, B. E. and THOMSON, K. J. The Heart in Pregnancy and the Childbearing Age. Boston, 1941. Little, Brown & Co.
104. HANKS, J. H. The mechanism of tuberculin hypersensitivity. *J. Immunol.*, 28: 105, 1935.
105. HARDGROVE, M., WHITTIER, L. and SMITH, E. R. Rheumatic fever on the Isthmus of Panama. *J. A. M. A.*, 130: 488, 1946.
106. HARRIS, T. N. Studies on the relation of the hemolytic streptococcus to rheumatic fever. III. Complement fixation versus streptococcal nucleoproteins with sera of patients with rheumatic fever. *J. Exper. Med.*, 87: 57, 1948.
107. HART, F. D. Rheumatic subcutaneous nodule formation. *Ann. Rheumat. Dis.*, 1: 196, 1939.
108. HARTLEY, G., JR. and LUSHBAUGH, C. C. Experimental allergic focal necrosis of the liver. *Am. J. Path.*, 18: 323, 1942.
109. HARTZ, P. H. and VAN DER SAR, A. Occurrence of rheumatic carditis in native population of Curacao, Netherlands West Indies. *Arch. Path.*, 41: 32, 1946.
110. HAWKING, F. Latent acute rheumatic carditis as determined at autopsy. *Arch. Int. Med.*, 54: 799, 1934.
111. HAWN, C. VAN Z. and JANEWAY, C. A. Histological and serological sequences in experimental hypersensitivity. *J. Exper. Med.*, 85: 571, 1947.
112. HEIDELBERGER, M. and KENDALL, F. E. A quantitative theory of the precipitin reaction. III. The reaction between crystalline egg albumin and its homologous antibody. *J. Exper. Med.*, 62: 697, 1935.
113. HEILMAN, D. H. and FELDMAN, W. H. Specific cytotoxic action of tuberculin. Studies on tissue of tuberculous rabbits in which negative cutaneous reactions to tuberculin have developed. *Am. Rev. Tuberc.*, 54: 312, 1946.
114. HELPERN, M. and TRUBEK, M. Necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis. *Arch. Path.*, 15: 35, 1933.
115. HENCH, P. S. et al. Rheumatism and arthritis. Ninth rheumatism review. *Ann. Int. Med.*, 28: 66 and 309, 1948.

115*a*. HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H. and POLLEY, H. F. The effects of a hormone of the adrenal cortex (compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Preliminary report. *Proc. Staff Meet., Mayo Clin.*, 24: 181, 1949.

116. HERRY. Contribution a l'étude du rheumatisme articular aigu; essai de pathogénie et de sérothérapie; étude clinique, anatomique et experimentale. *Bull. Acad. roy. de méd. de Belgique*, 28: 76, 1914.
117. HITCHCOCK, C. H., CAMERO, A. R. and SWIFT, H. F. Perivascular reactions in lung and liver following intravenous injection of streptococci into previously sensitized animals. *J. Exper. Med.*, 59: 283, 1934.
118. HOLBROOK, W. P. The Army Air Forces rheumatic fever control program. *J. A. M. A.*, 126: 84, 1944.
119. HOMBURGER, F. Sodium salicylate inhibiting anti-Rh immunization in animals. *Proc. Soc. Exper. Biol. & Med.*, 61: 101, 1945.
120. HOWE, H. A. and BODIAN, D. Second attacks of poliomyelitis. An experimental study. *J. Exper. Med.*, 74: 145, 1941.
121. HUEPER, W. C. and LANDSBERG, J. W. Experimental studies in cardiovascular pathology. I. Pathologic changes in the organs of rats produced by chronic nitrite poisoning. *Arch. Path.*, 29: 633, 1940.
122. HUMPHREY, J. H. Antigenic properties of hyaluronic acid. *Biochem. J.*, 37: 460, 1943.
123. HYDE, R. R. Complement interference—a new explanation for the Neisser-Wechsberg phenomenon. *Am. J. Hyg.*, 8: 730, 1928.
124. JAGER, B. V. and NICKERSON, M. The altered response of human beings to the intramuscular administration of typhoid vaccine during massive salicylate therapy. *Am. J. Med.*, 3: 408, 1947.
125. JENNINGS, G. Streptococcus surveys. News letter. Army Air Forces Rheumatic Fever Control Program. 1944–45.
126. JOKL, E. and MELZER, L. Rheumatic fever following athletic trauma. *Acta med. orient.*, 6: 9, 1947.
127. JONES, L. and FLEISCHER, M. S. The relation of serum protein fractions to serum sickness in rabbits. *J. Immunol.*, 26: 455, 1934.
128. KABAT, E. A. The immunochemistry of the proteins. *J. Immunol.*, 47: 513, 1943.
129. KABAT, E. A. Quantitative immunochemical aspects of some allergic reactions. *Am. J. Med.*, 3: 535, 1947.
130. KABAT, E. A., MOORE, D. H. and LANDOW, H. An electrophoretic study of the protein components in cerebrospinal fluid and their relationship to the serum proteins. *J. Clin. Investigation*, 21: 571, 1942.
131. KABAT, E. A., WOLF, A. and BEZAR, A. E. The rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants. *J. Exper. Med.*, 85: 117, 1947.
132. KALBAK, K. Splenectomi som aktwerende factor ved gigtfeber. *Nord. med.* (*Hospitalstidende*), 25: 427, 1945.
133. KALBAK, K. Hemolytic streptococci as an aetiological factor in rheumatic fever and rheumatoid arthritis. Programme, 1st European Rheumatology Congress, Copenhagen, 1947.
134. KEEFER, C. S., MYERS, W. K. and OPPEL, T. W. Streptococcal agglutinins in patients with rheumatoid (atrophic) arthritis and acute rheumatic fever. *J. Clin. Investigation*, 12: 267, 1933.
135. KEIL, H. The rheumatic subcutaneous nodules and simulating lesions. *Medicine*, 17: 261, 1938.
136. KELLET, C. E. and THOMSON, J. G. Complementary activity of blood serum in nephritis. *J. Path. & Bact.*, 48: 519, 1939.

137. KENDALL, F. E., HEIDELBERGER, M. and DAWSON, M. H. A serologically inactive polysaccharide elaborated by mucoid strains of group A hemolytic streptococcus. *J. Biol. Chem.*, 118: 61, 1937.

138. KIDD, J. G. and FRIEDEWALD, W. F. Natural antibody that reacts in vitro with sedimentable constituent of normal tissue cells. *J. Exper. Med.*, 76: 543, 1942.

139. KLEMPERER, P. The pathogenesis of lupus erythematosus and allied conditions. *Ann. Int. Med.*, 28: 1, 1948.

140. KLINGE, F. Die Eiweissüberempfindlichkeit (Gewebsanaphylaxie) der Gelenke. *Beitr. z. path. Anat. u. z. allg. Path.*, 83: 185, 1929.

141. KLINGE, F. Der Rheumatismus. München, 1933. J. F. Bergmann.

142. KLOTZ, O. Arterial lesions associated with rheumatic fever. *J. Path. & Bact.*, 18: 259, 1913.

143. KLOTZ, O. Periarteritis nodosa. *J. M. Research*, 37: 1, 1917.

144. KUCZNYSKI, M. H. and WOLFF. Beitrag zur Pathologie der experimentellen Streptokokkeninfektion der Maus (Milz, Leber, Herz). *Verhandl. d. deutsch. path. Gesellsch.*, 18: 47, 1921.

145. KUTTNER, A. G. and REYERSBACH, G. The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide. *J. Clin. Investigation*, 22: 77, 1943.

146. KUTTNER, A. G. and KRUMWIEDE, E. Observations on the effect of streptococcal upper respiratory infections on rheumatic children: a three-year study. *J. Clin. Investigation*, 20: 273, 1941.

147. LANCEFIELD, R. C. Specific relationship of cell composition to biological activity of hemolytic streptococci. *Harvey Lect.*, 36: 251, 1940–41.

148. LANDSTEINER, K. The Specificity of Serological Reactions. Cambridge, 1946. *Harvard Univ. Press.*

149. LANDSTEINER, K. and CHASE, M. W. Experiments on the transfer of cutaneous sensitivity to simple compounds. *Proc. Soc. Exper. Biol. & Med.*, 49: 688, 1942.

149*a*. LEGER, J., LEITH, W. and ROSE, B. Effect of adrenocorticotrophic hormone on anaphylaxis in the guinea pig. *Proc. Soc. Exper. Biol. & Med.*, 69: 465, 1948.

150. LEUCHTENBERGER, R. and SICHER, G. Visceral lesions following single subcutaneous injection of benzpyrene in mice. *Arch. Path.*, 31: 189, 1941.

151. LEVY, R. L., STROUD, W. D. and WHITE, P. D. Report of reexamination of 4,994 men disqualified for general military service because of the diagnosis of cardiovascular defects. *J. A. M. A.*, 123: 937 and 1029, 1943.

152. LEWIS, P. A. and LOOMIS, D. Allergic irritability; ulcerative types as determined by inheritance and as related to natural resistance against tuberculosis; experimental study on inbred guinea pigs. *J. Exper. Med.*, 47: 449, 1928.

153. LOEWE, L. and LENKE, S. Cardiac lesions resembling Aschoff bodies in rabbits. *J. Exper. Med.*, 71: 89, 1940.

154. LOEWENSTEIN, E. Rheumatic diseases and tuberculosis. *Am. Rev. Tuberc.*, 49: 58, 1944.

155. LONGCOPE, W. T. The production of experimental nephritis by repeated protein intoxication. *J. Exper. Med.*, 18: 678, 1913.

156. LONGCOPE, W. T. Effect of repeated injections of foreign protein on the heart muscle. *Arch. Int. Med.*, 15: 1079, 1915.

157. LONGCOPE, W. T. Serum sickness and analogous reactions from certain drugs, particularly the sulfonamides. *Medicine*, 22: 251, 1943.

158. LONGCOPE, W. T. and RACKEMANN, F. M. The relation of circulating antibodies to serum disease. *J. Exper. Med.*, 27: 341, 1918.

159. LUCIC, H. Uveal tissue sensitization in rabbits by synergic action of staphylotoxin. *Proc. Soc. Exper. Biol. & Med.*, 40: 273, 1939.

160. LURIE, M. B. Heredity, constitution and tuberculosis. An experimental study. *Am. Rev. Tuberc.*, supp. 3, vol. 46, Sept., 1941.

161. LURIE, M. B. Studies on the mechanism of immunity in tuberculosis. The fate of tubercle bacilli ingested by mononuclear phagocytes derived from normal and immunized animals. *J. Exper. Med.*, 75: 247, 1942.

162. LYTTLE, J. The Addis sediment count in scarlet fever. *J. Clin. Investigation*, 12: 95, 1933.

163. MCBROOM, J., SUTHERLAND, D. A., MOTE, J. R. and JONES, T. D. Effect of acute scurvy on the guinea pig heart. *Arch. Path.*, 23: 20, 1937.

164. MACCALLUM, W. G. Rheumatism. *J. A. M. A.* 84: 1545, 1925.

165. MCEWEN, C. Cytologic studies on rheumatic fever. I. Characteristic cell of the rheumatic granuloma. *J. Exper. Med.*, 55: 745, 1932.

166. MCEWEN, C. Cytologic studies on rheumatic fever. II. Cells of rheumatic exudates. *J. Clin. Investigation*, 14: 190, 1935.

167. MCMASTER, P. D. and HUDACK, S. S. Formation of agglutinins within lymph nodes. *J. Exper. Med.*, 61: 783, 1935.

168. MACNEAL, W. J., BLEVINS, A., SLAVKIN, A. E. and SCANLON, H. Experimental verrucous endocarditis. *Science*, 101: 415, 1945.

169. MACKENZIE, G. M. and HANGER, F. M. Allergic reactions to streptococcus antigens. *J. Immunol.*, 13: 41, 1927.

170. MACKENZIE, G. M. and LEAKE, W. H. Relation of antibody and antigen to serum disease susceptibility. *J. Exper. Med.*, 33: 601, 1921.

171. MAGRASSI, F. Experimental infectious rheumatism and streptococcal focal infection. *Acta rheumatol.*, 5: 2, 1933.

172. MALINER, M. M. and AMSTERDAM, S. D. Oral penicillin in the prophylaxis of recurrent rheumatic fever. *J. Pediatrics*, 31: 658, 1947.

173. MALLORY, G. K. and KEEFER, C. S. Tissue reactions in fatal cases of Streptococcus hemolyticus infection. *Arch. Path.*, 32: 334, 1941.

174. MASSELL, B. F. and JONES, T. D. The effect of sulfanilamide on rheumatic fever and chorea. *New England J. Med.*, 218: 876, 1938.

175. MASSELL, B. F., MOTE, J. R. and JONES, T. D. The artificial induction of subcutaneous nodules in patients with rheumatic fever. *J. Clin. Investigation*, 16: 125, 1937.

176. MASTER, A. M. and ROMANOFF, A. Treatment of rheumatic fever patients with and without salicylates. *J. A. M. A.*, 98: 1978, 1932.

177. MASUGI, M. Über die experimentelle Glomerulonephritis durch das spezifische Antinierenserum *Beitr. path. Anat. u. allg. Path.*, 92: 429, 1933–34.

178. Masugi, M., Murasawa, S. and Ya Shu. Über das Vorkommen von Aschoffschen Knötchen in Phthisikerherzen. *Virchows Arch. f. path. Anat.*, 299: 426, 1937.

179. Mayer, M. M., Osler, A. G., Bier, O. G. and Heidelberger, M. The activating effect of magnesium and other cations on the hemolytic function of complement. *J. Exper. Med.*, 84: 535, 1946.

180. Medical Research Council: Social Conditions and Acute Rheumatism. London, 1927. His Majesty's Stationery Office.

181. Menne, F. R., Jones, O. N. and Jones, N. W. Changes in the myocardium of rabbits from augmenting the heart rate mechanically and from induced hyperthyroidism. *Arch. Path.*, 17: 333, 1934.

182. Metz, W. Die geweblichen Reaktionserscheinungen an der Gefässwand bei hypergischen Zuständen und deren Beziehungen zur Periarteritis nodosa. *Beitr. z. path. Anat. u. z. allg. Path.*, 88: 17, 1932.

183. Meyer, K. The biological significance of hyaluronic acid and hyaluronidase. *Physiol. Rev.*, 27: 335, 1947.

184. Migounov, B. I. Sur le phénomeňe intravasculaire de la réaction hyperergique. *Acta Rheumatol.*, no. 23, p. 9, 1934.

185. Miller, C. P., Jr. Spontaneous interstitial myocarditis in rabbits. *J. Exper. Med.*, 40: 543, 1924.

186. Mirsky, I. A. Artificial induction of subcutaneous nodules in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 143, 1945.

187. Moen, J. K. Tissue culture studies on bacterial hypersensitivity. II. Reactions of tissues from guinea pigs infected with group A hemolytic streptococci. *J. Exper. Med.*, 64: 355, 1936.

188. Moen, J. K. and Swift, H. F. Tissue culture studies on bacterial hypersensitivity. *J. Exper. Med.*, 64: 339, 1936.

189. Morgan, I. M. Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue. *J. Exper. Med.*, 85: 131, 1947.

190. Morgan, I. M. The role of antibody in experimental poliomyelitis. III. Distribution of antibody in and out of the central nervous system in paralyzed monkeys. *Am. J. Hyg.*, 45: 390, 1947.

191. Mote, J. R. and Jones, T. D. Studies of hemolytic streptococcal antibodies in control groups, rheumatic fever and rheumatoid arthritis. *J. Immunol.*, 41: 35, 1941.

192. Myers, W. K., Keefer, C. S. and Holmes, W. F. The resistance to fibrinolytic activity of the hemolytic streptococcus with special reference to patients with rheumatic fever and rheumatoid (atrophic) arthritis. *J. Clin. Investigation*, 14: 119, 1935.

193. Nedzel, A. J. Experimental endocarditis. I. Endothelial changes due to pressor episodes. *Arch. Path.*, 24: 143, 1937.

194. Nye, R. and Parker, F., Jr. Tissue reactions in rabbits following intravenous injection of bacteria. *Am. J. Path.*, 6: 381, 1930.

195. Oeller, H. Experimentelle Studien zur pathologischen Physiologie des Mesenchyms und seiner Stoffwechselleistungen bei Infektionen. *Krankheitsforschung*, 1: 28, 1925.

196. Opie, E. L. Pathogenesis of the specific inflammatory reaction of immunized animals (Arthus phenomenon). The relation of local "sensitization" to immunity. *J. Immunol.*, 9: 259, 1924.

197. Opie, E. L. The significance of allergy in disease. *Medicine*, 15: 489, 1936.

198. Pappenheimer, A. M. and von Glahn, W. C. Studies in the pathology of rheumatic fever. *Am. J. Path.*, 3: 583, 1927.

199. Paul, J. R. The Epidemiology of Rheumatic Fever. 2nd ed. New York, 1943. The Metropolitan Life Insurance Co.

200. Pearce, J. M. Cardiac lesions in rabbits produced by a filterable virus (Virus III). *Arch. Path.*, 28: 827, 1939.

201. Peck, J. L. and Thomas, L. Failure to produce lesions or auto-antibodies in rabbits by injecting tissue extracts, streptococci and adjuvants. *Proc. Soc. Exper. Biol. & Med.*, 69: 451, 1948.

202. Pemberton, R., Eiman, J., Patterson, F. M. S. and Stackhous, E. A. Attempts at the experimental production of arthritis. *J. Lab. & Clin. Med.*, 32: 1121, 1947.

203. Penna de Azevedo, A. Incidencia do reumatismo no Rio de Janeiro. *Mem. Inst. Oswaldo Cruz*, 42: 177, 1945.

204. von Pirquet, C. and Schick, B. Die Serumkrankheit. Leipzig, 1905.

205. Poynton, F. J. and Paine, A. Researches on Rheumatism. London, 1913. J. A. Churchill, Ltd.

206. Rachmilewitz, M. and Silberstein, W. The amount of complement in the blood in rheumatic fever and rheumatoid arthritis. *J. Lab. & Clin. Med.*, 22: 1240, 1937.

206*a*. Ragan, C., Grokoest, A., and Boots, R. H. Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis. *Am. J Med.*, 7: 741, 1949.

207. Rantz, L. A., Boisvert, P. J. and Spink, W. W. Etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.*, 76: 131, 1945.

208. Rantz, L. A. and Randall, E. Antibacterial precipitating antibodies in group A hemolytic streptococcus sore throat. *Am. J. Med.*, 2: 551, 1947.

209. Rantz, L. A., Spink, W. W. and Boisvert, P. J. Abnormalities of the electrocardiogram following hemolytic streptococcus sore throat. *Arch. Int. Med.*, 77: 66, 1946.

210. Revenna, P. Review of recent Italian work on rheumatism. *Ann. Rheum. Dis.*, 1: 167, 1939.

211. van Ravenswaay, A. C. The geographic distribution of hemolytic streptococci. *J. A. M. A.*, 126: 486, 1944.

212. Read, F. E. M., Ciocco, A. and Taussig, H. B. The frequency of rheumatic manifestations among the siblings, parents, uncles, aunts and grandparents of rheumatic and control patients. *Am. J. Hyg.*, 27: 719, 1938.

213. Reyersbach, G., Lenert, T. F. and Kuttner, A. G. An epidemic of influenza B occurring in a group of rheumatic children concurrent with an outbreak of streptococcal pharyngitis: clinical and epidemiological observations. *J. Clin. Investigation*, 20: 289, 1941.

214. Rich, A. R. Hypersensitivity in disease. *Harvey Lect.*, 42: 106, 1946–47.

215. Rich, A. R. and Follis, R. H., Jr. Studies on the site of sensitivity in the Arthus phenomenon. *Bull. Johns Hopkins Hosp.*, 66: 106, 1940.

216. Rich, A. R. and Gregory, J. E. Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 73: 239, 1943.

217. Rich, A. R. and Lewis, M. R. Mechanism of allergy in tuberculosis. *Proc. Soc. Exper. Biol. & Med.*, 25: 296, 1927–28 and *Bull. Johns Hopkins Hosp.*, 50: 115, 1932.

218. Rinehart, J. F., Greenberg, L. D., Olney, M. B. and Choy, F. Metabolism of vitamin C in rheumatic fever. *Arch. Int. Med.*, 61: 552, 1938.

219. Rinehart, J. F. and Mettier, S. R. The heart valves and muscle in experimental scurvy with superimposed infection, with notes on the similarity of the lesions to those of rheumatic fever. *Am. J. Path.*, 10: 61, 1934.

220. Roessle, R. Die morphologischen Aequivalente der Allergie. *Acta rheumatol.*, 8: 64, 1936.

220*a*. Rothpard, S., Watson, R. F., Swift, H. F. and Wilson, A. In press.

221. Rutstein, D. D. and Walker, W. H. Complement activity in pneumonia. *J. Clin. Investigation*, 21: 347, 1942.

222. Sabin, A. B. Experimental proliferative arthritis in mice produced by filterable, pleuropneumonia-like microorganisms. *Science*, 89: 228, 1939.

223. Sabin, F. R. Cellular reactions to tuberculo-proteins compared with reactions to tuberculo-lipids. *J. Exper. Med.*, 68: 837, 1938.

224. Schlesinger, G. Relationship of throat infection to acute rheumatism in childhood. *Arch. Dis. Childhood*, 5: 411, 1930.

225. Schlesinger, B., Signy, A. G., Amies, C. R. and Barnard, J. E. Aetiology of acute rheumatism. Experimental evidence of a virus as the causal agent. *Lancet*, 1: 1145, 1935.

226. Schultz, M. P. Cardiovascular and arthritic lesions in guinea pigs with chronic scurvy and hemolytic streptococcic infections. *Arch. Path.*, 21: 472, 1936.

227. Schultz, M. P. Allergic irritability in rheumatic and nephritic patients. *Pub. Health Rep.*, 54: 1273, 1939.

228. Schwentker, F. F. and Comploier, F. C. Production of kidney antibodies by injection of homologous kidney plus bacterial toxins. *J. Exper. Med.*, 70: 223, 1939.

229. Seastone, C. V. The virulence of group C hemolytic streptococci of animal origin. *J. Exper. Med.*, 70: 361, 1939.

230. Seegal, B. C. Anaphylaxis. Chapt. 6. Gay and Associates, 1935.

231. Seegal, B. C. and Loeb, E. N. The production of chronic glomerulonephritis in rats by the injection of rabbit anti-rat-placenta serum. *J. Exper. Med.*, 84: 211, 1946.

232. Seegal, D., Heidelberger, M., Jost, E. L. and Lyttle, J. D. Precipitins against fractions of streptococci in hemolytic streptococcus disease, glomerular nephritis, rheumatoid arthritis and S. viridans endocarditis. *Proc. Soc. Exper. Biol. & Med.*, 30: 582, 1933.

233. Seegal, D., Heidelberger, M. and Jost, E. L. The formation of precipitin for the group A specific carbohydrate of Streptococcus hemolyticus in rabbits injected intravenously and subcutaneously. *J. Immunol.*, 27: 211, 1934.

234. Seegal, D. and Seegal, B. C. Local organ hypersensitiveness. I. Experimental production in the rabbit eye. *Proc. Soc. Exper. Biol. & Med.*, 27: 390, 1930.

235. Seegal, D., Seegal, B. C. and Jost, E. L. The Arthus phenomenon. Local anaphylactic inflammation in rabbit pericardium, heart and aorta. *J. Exper. Med.*, 55: 155, 1932.

236. Seegal, D., Seegal, B. C. and Jost, E. L. A comparative study of the geographic distribution of rheumatic fever, scarlet fever and acute glomerulonephritis in North America. *Am. J. M. Sc.*, 190: 383, 1935.

237. Selye, H. The general adaptation syndrome and the diseases of adaptation. *J. Clin. Endocrinol.*, 6: 117, 1946.

238. Sherman, W. B. Drug allergy. *Am. J. Med.*, 3: 586, 1947.

239. Siegmund, H. Über einige Reaktionen der Gefässwände und des Endokards bei experimentellen und menschlichen Allgemeininfektionen. *Verhandl. d. deutsch. path. Gesellsch.*, 20: 260, 1925.

240. Smadel, J. E. and Farr, L. E. Experimental nephritis in rats induced by injection of anti-kidney serum. *J. Exper. Med.*, 65: 527 and 541, 1937.

241. Small, J. C. Observations bearing on the specificity of streptococcus cardioarthritidis in rheumatic fever and Sydenham's chorea. *Am. J. M. Sc.*, 175: 638, 1928.

241*a*. Stoerk, H. C. Personal communication.

242. Swift, H. F. The action of sodium salicylate upon the formation of immune bodies. *J. Exper. Med.*, 36: 735, 1922.

243. Swift, H. F. Pathogenesis of rheumatic fever. *J. Exper. Med.*, 39: 497, 1924.

244. Swift, H. F. Rheumatic fever. *J. A. M. A.*, 92: 2071, 1929.

245. Swift, H. F. Rheumatic heart diseases. Pathogenesis and etiology in their relation to therapy and prophylaxis. *Medicine*, 19: 417, 1940.

245*a*. Swift, H. F. The etiology of rheumatic fever. Thirtieth annual session Am. College of Physicians. New York, April 1, 1949.

246. Swift, H. F. and Brown, T. M. Pathogenic, pleuropneumonia-like microorganisms from acute rheumatic exudates and tissues. *Science*, 89: 271, 1939.

247. Swift, H. F., Derick, C. L. and Hitchcock, C. H. Bacterial allergy (hyperergy) to non-hemolytic streptococci in its relation to rheumatic fever. *J. A. M. A.*, 90: 906, 1928.

248. Swift, H. F. and Hodge, B. E. Type-specific anti-M precipitins in rheumatic and nonrheumatic patients with hemolytic streptococcus infections. *Proc. Soc. Exper. Biol. & Med.*, 34: 849, 1936.

249. Swift, H. F., Hitchcock, C. H., Derick, C. L. and McEwen, C. Intravenous vaccination with streptococci in rheumatic fever. *Tr. A. Am. Physicians*, 45: 247, 1930.

250. Swift, H. F. and McEwen, C. Rheumatic Fever. Oxford Medicine. Vol. v, London, 1938. Oxford Univ. Press.
251. Swift, H. F., Moen, J. K. and Hirst, G. K. The action of sulfanilamide in rheumatic fever. *J. A. M. A.*, 110: 426, 1938.
252. Swift, H. F. and Schultz, M. P. The synergic action of staphylotoxin and beef lens extract in rabbits. *J. Exper. Med.*, 63: 703, 1936.
253. Swift, H. F., Wilson, M. G. and Todd, E. W. Skin reactions of patients with rheumatic fever to toxic filtrates of streptococcus. *Am. J. Dis. Child.*, 37: 98, 1929.
254. Tal alajew, W. T. Der akute Rheumatismus. *Klin. Wchnschr.*, 1: 124, 1929.
255. Taran, L. M., Jablon, J. M. and Weyr, H. N. Cutaneous response to type specific proteins of homolytic streptococci. *J. Immunol.*, 51: 53, 1945.
256. Taran, L. M., Jablon, J. M. and Weyr, H. N. Antistreptolysin patterns in rheumatic children. *J. Immunol.*, 53: 381, 1946.
257. Thomas, C. B. and France, R. A preliminary report of the prophylactic use of sulfanilamide in patients susceptible to rheumatic fever. *Bull. Johns Hopkins Hosp.*, 64: 67, 1939.
258. Thompson, R., Gallardo, E. and Khorazo, D. Precipitins in the ocular tissues of rabbits generally and locally immunized with crystalline egg albumin. *Am. J. Ophth.*, 19: 852, 1936.
259. Thomson, S. and Glazebrook, A. J. Infectious diseases in a semi-closed community. *J. Hyg.*, 41: 570, 1941.
260. Tillett, W. S., Edwards, L. B. and Garner, R. L. Fibrinolytic activity of hemolytic streptococci. The development of resistance to fibrinolysis following acute hemolytic streptococcus infections. *J. Clin. Investigation*, 13: 47, 1934.
261. Todd, E. W. Antigenic streptococcal hemolysin. *J. Exper. Med.*, 55: 267, 1932.
262. Todd, E. W., Laurent, L. J. M. and Hill, N. G. Streptococcal antitoxin and antistreptolysin. *J. Path. & Bact.*, 36: 201, 1933.
263. Todd, E. W., Coburn, A. F. and Hill, A. B. Antistreptolysin S titres in rheumatic fever. *Lancet*, 2: 1213, 1939.
264. Topley and Wilson. Principles of Bacteriology and Immunity. Revised by Wilson, G. S. and Miles, A. A. Baltimore, 1946. Williams & Wilkins Co.
265. Treffers, H. P., Heidelberger, M. and Freund, J. Antiproteins in horse sera. iv. Antibodies to rabbit serum globulin and their interaction with antigen. *J. Exper. Med.*, 86: 95, 1947.
266. Tsuda, S. Experimentelle Untersuchungen über die entzündliche Reaktion der Subcutis in Beziehung zum individuellen Immunitätszustand. *Virchows Arch. f. path. Anat.*, 247: 123, 1923.
267. Vaubel, E. Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes. *Beitr. z. path. Anat. u. z. allg. Path.*, 89: 374, 1932.
268. Veil, W. H. and Buchholz, B. Der Komplementschwund im Blute. *Klin. Wchnschr.*, 11: 2019, 1932.
269. Walsh, T. E., Sullivan, F. L. and Cannon, P. R. Local formation of antibody by the nasal mucosa. *Proc. Soc. Exper. Biol. & Med.*, 29: 675, 1932.
270. Wasson, V. P. and Brown, E. E. Immunization against rheumatic fever. *J. Pediat.*, 23: 24, 1943.
271. Watson, R. F., Rothbard, S. and Swift, H. F. The relationship of postscarlatinal arthritis and carditis to rheumatic fever. *J. A. M. A.*, 128: 1145, 1945.
272. Wedum, A. G. and Wedum, B. G. Rheumatic fever in Cincinnati in relation to rentals, crowding, density of population and negroes. *Am. J. Pub. Health*, 34: 1065, 1944.
273. Wedum, A. G. and Wedum, B. G. Serum precipitation reaction in rheumatic fever and in other conditions. *Proc. Soc. Exper. Biol. & Med.*, 61: 432, 1946.
274. Weil, A. J. The Wassermann antigen and related "alcohol-soluble" antigens. *Bact. Rev.*, 5: 293, 1941.
275. Weintraud, W. Ueber die Pathogenese des akuten Gelenkrheumatismus. *Berl. klin. Wchnschr.*, No. 30, 1381, 1913.
276. Westphal, Wassermann and Malkoff. Ueber den infectiösen Charakter und den Zusammenhang von acutem Gelenkrheumatismus und Chorea. *Berl. klin. Wchnschr.*, no. 29, p. 638, 1899.
277. Wilens, S. L., Pearce, J. M. and Fallas Diaz, M. Relative incidence of rheumatic valve disease in New York and Costa Rica and its bearing on the rheumatic origin of calcareous aortic stenosis. *Am. Heart J.*, 30: 573, 1945.
278. Wilens, S. L. and Sproul, E. E. Spontaneous cardiovascular disease in rats. ii. Lesions of the vascular system. *Am. J. Path.*, 14: 201, 1938.
279. Wilson, K. S. and Alexander, H. L. The relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. *J. Lab. & Clin. Med.*, 30, 195, 1945.
280. Wilson, M. G. Rheumatic Fever. New York, 1940. The Commonwealth Fund.
281. Wilson, M. G. and Swift, H. F. Intravenous vaccination with hemolytic streptococci. *Am. J. Dis. Child.*, 42: 42, 1931.
282. Winblad, S. Studies in haemolytic streptococcus fibrinolysin, antifibrinolysin and antistreptolysin (with particular reference to rheumatic fever). *Acta path. et Microbiol. Scandinav.*, Supp. 44, 1941.
283. Wu, T. T. Ueber Fibrinoidbildung der Haut nach unspezifischer Gewebsschaedigung bei der Ratte. *Virchows. Arch. f. path. Anat.*, 300: 373, 1937.
284. Zinsser, H. Studies on the tuberculin reaction and on specific hypersensitiveness in bacterial infection. *J. Exper. Med.*, 34: 495, 1921.
285. Zinsser, H. and Enders, J. F. Variations in the susceptibility of guinea pig to reversed passive anaphylaxis. *J. Immunol.*, 30: 327, 1936.
286. Zinsser, H., Enders, J. F. and Fothergill, L. D. Immunity: Principles and Application in Medicine and Public Health. New York, 1939. The Macmillan Co.
287. Zinsser, H. and Grinnell, F. B. Further studies on bacterial allergy. Allergic reactions to the hemolytic streptococcus. *J. Immunol.*, 10: 725, 1925.
288. Zuger, B. Group infection and immunity during a scarlet fever epidemic in a boys' school. *Am. J. Hyg.*, 21: 588, 1935.

Seminars on Antibiotics

Bacitracin*

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THE antibiotic, bacitracin, is produced by the Tracey I strain of Bacillus subtilis which was discovered in June, 1943, in the Laboratory of Bacteriological Research of the Department of Surgery, College of Physicians and Surgeons, Columbia University.[1] The organism was recovered from the damaged tissue and street dirt débrided from the compound fracture of a seven year old child by the name of Tracey. The antibiotic was therefore named "bacitracin."

PROPERTIES OF THE ORGANISM AND ITS FILTRATE

Dr. Kenneth Burdon of Baylor University has studied the cultural characteristics of this organism and has classified it as a B. licheniformis but as far as the authors know, no other strain of this species has been found able to produce this antibiotic. The active principle is secreted into any medium in which the organism will grow but the amount of the antibiotic depends upon the composition of the medium, the condition of the seed cultures and the circumstances of incubation. The organism forms a thick pellicle on the surface of the media but very little active principle can be obtained from this bacterial mass. The active agent is readily obtained in the filtrate of the decanted media after passage through a Chamberland, Berkefeld, Selas or Seitz filter.

Preliminary studies of the filtrate showed that it had a powerful antibiotic action with a wide antibacterial spectrum. (Table I.) When produced on a glutamic acid synthetic medium, bacitracin showed no toxicity when injected into laboratory animals in fairly large quantities over a long period of time. It was then found to be non-toxic and non-irritating when injected in small quantities into human beings. It was found to be capable of controlling experimental hemolytic streptococcal peritonitis in mice when injected subcutaneously several hours after the intraperitoneal injection of the organisms, thus indicating that it was absorbed and could reach an area of infection some distance away from the site of injection. It was also able to prevent gas gangrene following the intramuscular injection of Clostridium welchii in guinea pigs.[1] Furthermore, it was capable of promptly controlling infections such as furuncles, carbuncles and superficial abscesses when injected into the center of such lesions in human beings.

The extraction and partial purification of bacitracin was carried out by Dr. Herbert Anker of the Department of Biochemistry with the advice and counsel of Professor Hans Clarke. These studies were reported by Anker, Johnson, Goldberg and Meleney in 1948.[2]

CHEMICAL PROPERTIES OF LABORATORY BACITRACIN

The chemical properties of the laboratory product were found to be as follows:

Stability. Partially purified neutral or slightly acid (pH 6.6) aqueous concentrates of bacitracin prepared by the butanol

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method showed no detectable change in titer after storage for eight months to one year at temperatures of 0° to 5°C. At room temperature there was a loss of 30 to 50 per cent of the activity after a two weeks' storage period but neutral, inorganic salt-free solutions were dried at room temperature without loss of activity. Inactivation was complete after two weeks at 35° to 37°C. Bacitracin solutions were stable to normal hydrochloric acid at 0° to 5°C and to 0.01 normal hydrochloric acid at both 0° to 5°C and 37°C. They were rapidly inactivated in alkaline solution above pH 9 at both temperatures. In the presence of hydrogen peroxide there was complete loss of antibiotic activity. In 1947 Scudi et al. found that bacitracin was partially inactivated by BAL and sodium thiosulfate.[3]

Solubility. The laboratory product of bacitracin was found to be soluble in methanol, ethanol, isopropanol, *n*-butanol and cyclohexanol, slightly soluble in cyclohexanone, and insoluble in other organic solvents such as ether, chloroform, benzene, acetone and ethyl acetate. In aqueous solution the activity was diffusible through a nitrocellulose membrane which holds back particles of molecular weight 2,000.

Precipitability. 1. *Metal ions:* Bacitracin was precipitated by salts of heavy metals. This precipitation was accompanied by inactivation if the heavy metal ions, low in the electromotive series, were used. On the other hand, the action of zinc ions, high in the electromotive series, did not result in inactivation but precipitation of the active material was incomplete.

2. *Organic acids:* Several organic acids were found to precipitate the activity from concentrates, namely, trichloracetic, tannic, azobenzene-*p*-sulfonic, benzoic, furoic and salicylic acids. With the first two, considerable activity disappeared during the isolation of the bacitracin. The results with benzoic acid were variable. Large quantities of furoic acid were required to precipitate the antibiotic and the percentage of recovery was low. Salicylic acid, however, yielded precipitates with all batches tested; the yields were high and no inactivation was observed.

3. *Other precipitants:* Bacitracin was also precipitated from water solution by high concentrations of sodium chloride, acetone, ammonium rhodanilate, Reinecke's salt and molybdic acid.

Adsorption. Bacitracin was found to be adsorbed on charcoal, Lloyd's reagent and aluminum oxide but the problem of elution had not then been solved.

These preliminary studies clearly indicated the necessity for the further production, purification and clinical appraisal of bacitracin. In order to carry this out it was decided to call upon one of the commercial firms to produce it in large quantity.

COMMERCIAL PRODUCTION OF BACITRACIN

The first attempt to transfer production from laboratory to commercial methods was made by Lederle but difficulties were encountered and most of the antibiotic was lost during the process of extraction. It was then taken over by the Ben Venue Laboratories of Bedford, Ohio. After six months of experimentation a method was found which produced the antibiotic in soybean medium, yielding ten times the assay obtained from the synthetic medium. Furthermore, a shortcut was found in the extraction process by adsorbing the antibiotic on charcoal and eluting it with dilute hydrochloric acid. The original method of growth on the surface of the medium was continued and in the course of a year a stable, lyophilized, slightly yellowish white powder was obtained of sufficient purity to warrant a pharmacologic study.

During the various stages of development the commercial product* steadily increased in purity; even the early crude preparations were effective when applied to infected areas and surfaces. Experiences with the first hundred cases of surgical infections so treated served as the basis for a report by

* The commercial bacitracin used in these studies was supplied by the Ben Venue Laboratories of Bedford, O., and the Commercial Solvents Corporation of Terre Haute, Ind.

the authors which was published in March, 1947.[4]

These cases represented the general run of localized or localizing infections which are seen every day in any surgeon's office or any hospital clinic. Eighty-eight per cent of these patients responded favorably to the drug treatment. Bacteriologic studies revealed that the majority of surgical infections are due to a mixture of organisms. When the organisms associated with these infections were tested for sensitivity to bacitracin and penicillin, most of them were found to be susceptible to both. Thirty were susceptible to bacitracin and resistant to penicillin while only six were resistant to bacitracin and susceptible to penicillin. It was found that the daily aspiration of superficial or even deep abscesses followed by the instillation of bacitracin often caused rapid resolution of the process and often obviated surgical incision. Similarly, the application of a solution or ointment containing bacitracin in a concentration of 500 units per cc. of solution or Gm. of ointment to an infected wound or superficial ulcer often caused rapid disappearance of the infecting organisms and healing of the wound.

PHARMACOLOGIC STUDIES OF BACITRACIN

The pharmacologic studies were under the direction of Dr. John Scudi of the Department of Pharmacology of the College of Physicians and Surgeons, Columbia University, with the advice and counsel of Professor Harry B. van Dyke. These studies served as the basis for three reports which appeared in 1947.[3,5,6]

Acute toxicity experiments were carried out in Rockland Swiss mice and in Sherman rats. Several different lots of bacitracin were tested and it was found that the toxicity of the different lots varied independently of the activity and that the aforementioned lot was least toxic. It was also noted that inactivation of the material by incubation at 37°C. for eight days at a pH of 7 did not alter the toxicity of the preparation whereas its antibiotic activity was completely lost in that time. The only injury to any of the organs or tissues of the body was in the lower renal tubules with large doses of the antibiotic. Mice and to a lesser degree monkeys were affected whereas dogs and rats showed no injury to the kidneys. The subcutaneous LD-50 in mice was four to seven times the intraperitoneal LD-50 and lethal results were produced only with immense oral doses.

The absorption and excretion of bacitracin was studied in the dog. Significant concentration of the drug persisted in the blood stream as long as seven or eight hours after parenteral administration. Dogs showed no signs of toxicity even when doses as high as 6,000 units per Kg. of body weight were used, other than slight or transient vasodepressor effects produced by rapid intravenous injection. Recovery of the drug in the urine showed wide variations but in general it increased in direct ratio to the dose administered. However, significant concentrations of the drug could be found in the urine more than seven hours after the administration of a single dose of the antibiotic. Concentrations of 14 to 18 units per cc. could be found in dogs' urine seven hours after a single intramuscular injection of 1,000 units per Kg. and as high as 92 units per cc. after a 3,000 unit per Kg. dose. These figures for the urinary excretion of bacitracin following intramuscular administration are in sharp contrast to those after oral administration. Scudi could detect no bacitracin in the urine after a single oral dose of 3,000 to 6,000 units per Kg. The highest recovery reported by Bond et al.[7] after oral administration in the dog was 0.22 units per cc. after the 10,000 unit per Kg. dose, and 1.65 units per cc. after the 20,000-unit per Kg. dose.

Scudi also found that although bacitracin remained in the blood stream for many hours, it did not penetrate the red blood cells nor did it enter the spinal fluid freely. Following prolonged daily administration of crude bacitracin concentrates in dogs and monkeys there were no significant changes in blood morphology.

Concentrations of bacitracin of 6,000 units per cc., when injected into the abdominal skin of experimental rabbits, caused no irritation and there was no reaction to 1,200 units per cc. in the conjunctival sac of rabbits. There was some induration after repeated intramuscular injections into the dog while in the monkey there were at times small areas of necrosis of the muscle at the sites of the injections.

In the dog the urine samples remained negative for sugar and albumin but both of these appeared in the urine of monkeys. Large doses approximating the LD-50 produced some damage to the renal tubules in the mouse and occasionally in the monkey, but the lesions were insignificant in the rat and in the dog. Scudi considered the toxicity to be of the same order as that of streptomycin.

EARLIEST SYSTEMIC ADMINISTRATION OF BACITRACIN

With this preliminary demonstration of relatively low toxicity, it was deemed safe to start cautiously subcutaneous, intramuscular and mouth administration of bacitracin in human volunteers. It was found that blood and urine levels could be obtained by subcutaneous and intramuscular injections, but only urine levels and those of low degree when the drug was given by mouth. We then began cautiously to treat patients with intramuscular injections in gradually increasing doses ranging from 3,000 to 20,000 units every six hours. With all of these doses it was found that detectable blood levels of bacitracin could be found six hours after administration. In the first case of infection treated systemically the administration of 3,000 units every six hours was stopped on the third day when albuminuria appeared, but it promptly disappeared. Later cases with increased dosage showed a transient albuminuria and a few granular casts but these findings disappeared during the course of treatment and there were no clinical signs of toxicity. Furthermore, the infections for which these patients were treated, in most cases, came promptly under control.

With the same material Dr. Harry Eagle found that bacitracin had a lethal action on spirochetes and that he could cure his experimental rabbits with syphilis by its systemic administration. He also found that bacitracin had a lethal action on spirochetes directly proportional to its concentration, that it was slowly eliminated through the kidneys at the rate of glomerular filtration and that it had a striking synergistic action with penicillin in the cure of experimental syphilis.[8] Therefore, he started a study of the treatment of human syphilis with bacitracin alone and with bacitracin in combination with penicillin. The report of this study will be published elsewhere.[9]

During this period units were set up in several different cities for the clinical appraisal of bacitracin. These were organized by Dr. Alfred Longacre in New Orleans, Major Edwin J. Pulaski at Fort Sam Houston, Dr. Edward H. Reisner, Jr., at Bellevue Hospital in New York, Dr. Harold Zintel in Philadelphia and Dr. William Altemeier in Cincinnati, beside the unit already in operation at Presbyterian Hospital in New York under the direction of the authors of this paper.

The number of patients treated systemically during the spring, summer and fall of 1947 increased slowly because of the fact that production was delayed, not only in the Ben Venue Laboratories but also in the laboratories of the other manufacturers, all of whom encountered production difficulties. In December, 1947, the Commercial Solvents Corporation began to produce bacitracin by the deep tank method. By an agreement with the Ben Venue Laboratories the whole output and experience of Ben Venue in the production of bacitracin was turned over to the Commercial Solvents Corporation. Thereafter production by the surface growth method was given up and the deep tank method was employed. Bacitracin was produced by the Commercial Solvents Corporation only in small quantities during the months of December, Janu-

ary and February and extensive clinical observations were not made with it until the spring of 1948, inasmuch as it was decided to use up the available Ben Venue material first. The units in Philadelphia and San Antonio, which were started later than the others, had little or no experience with the Ben Venue material and their first patients were treated almost entirely with the Commercial Solvents product.

From August, 1946, to March, 1948, the systemic administration of bacitracin made by the Ben Venue Laboratories by the surface growth method was continued with increasing confidence in its efficacy and safety. The albuminuria and cylindruria had proved to be of a low order and in the majority of cases these signs of kidney irritation disappeared during the course of treatment or promptly after the cessation of treatment. Occasionally intramuscular injection was followed by nausea and in some cases by vomiting but this did not interfere with treatment except in one case, a paraplegic with a chronic decubital ulcer.

However, during this period an effort was made to remove all evidences of toxicity and we were encouraged by the fact that with the ultracentrifuge toxic products could be carried down to the heavy portion of the solution, while bacitracin was evenly distributed.

TENTATIVE F.D.A. SPECIFICATIONS FOR BACITRACIN

In January, 1948, at the request of the Surgeon General's Office, Dr. Henry Welch of the Food and Drug Administration, called a meeting in Washington of the commercial firms interested in the manufacture of bacitracin for the purpose of setting up specifications dealing with potency, solubility, stability, toxicity and pressor, depressor and pyrogenic effects. The most important specifications dealt with potency and toxicity and we recommended that a toxicity specification be set up at an LD-50 of 500 and an LD-0 of 250 units for a 20-G. mouse by intraperitoneal or intravenous injection, but the manufacturers claimed that this level would be difficult to attain and our clinical experience with the Ben Venue product seemed to indicate that lower figures would give a sufficient margin of safety. Therefore, toxicity levels were set at 200 units for the LD-50 and 100 units for the LD-0, with the understanding that further attempts would be made to raise these standards as the manufacturers improved their product.

FIRST CONFERENCE ON RESULTS OF BACITRACIN TREATMENT

In March, 1948, a meeting was called in New York at the Columbia-Presbyterian Medical Center to which the leaders of the study units and the manufacturers were invited for a full presentation of their experiences with bacitracin both in the laboratory and in the clinic. At that meeting Dr. Lyman Craig of the Rockefeller Institute gave a preliminary report on the purification of bacitracin by his countercurrent apparatus. He stated that the commercial product contained three organic substances and one inorganic. One of the organic substances predominated and this was made up of a number of amino acids. Chromatographic studies identified many of these.

By the time of the March meeting the number of surgical infections treated locally had reached 200 and favorable results had been obtained in 87 per cent of these cases. Furthermore, it was found that a fairly large number of the organisms associated with these infections were resistant to penicillin and susceptible to bacitracin. At the same time a large series of cases of dermatologic infections were reported by Dr. J. Lowry Miller.[10] The dermatologists were particularly impressed with the high rate of cure and the low incidence of allergic reactions to bacitracin as contrasted with penicillin and the sulfonamides.

Experiments were carried out with various bases in order to find one that would be more stable than the carbowax propylene glycol base previously used. Such bases were made primarily either with lanette wax or

with cetyl alcohol. These bases readily released the antibiotic and this did not deteriorate as rapidly at room temperature as it did in the carbowax base. In grease bases the bacitracin was still more stable but it was not as readily released from them.

A study of the development of resistance to bacitracin of susceptible bacteria was made during this period and it was found that a few strains slowly developed resistance but this was of a low order and of slow development. In dermatologic and local surgical infections this appeared to be inconsequential because it was easily overcome by the concentration of the antibiotic used with local application.

At the March meeting Dr. Alson Braley of the Department of Ophthalmology stated his belief that bacitracin was the treatment of choice in ophthalmic infections because of its effectiveness and the low incidence of allergic manifestations. Dr. Edward Reisner reported success in the systemic treatment of pneumonia at Bellevue Hospital. Dr. Harry Eagle of Baltimore discussed the preliminary steps in his study of bacitracin in the treatment of syphilis.

For the treatment of systemic infections the units had gathered data which were listed on carefully prepared summary sheets designed to permit the transfer of all important information regarding every case to punch cards for statistical analysis. Up to that time the unit at the Presbyterian Hospital had treated thirty patients with various types of infections and reports from the various units totaled approximately 100 cases of all types, both medical and surgical. All of the units which had been functioning for several months reported gratifying results in the treatment of infections and increasing confidence in the safety of the drug. The evidences of kidney irritation were minimal and transient and they did not interfere with the course of treatment. However, for the first time a disquieting note was struck by Major Pulaski, who noted that a few patients treated with the Commercial Solvents material made by the deep tank growth of the organism had shown more evidence of kidney damage than the other units had observed, as indicated by larger amounts of albumin in the urine and an increased number of granular casts, renal epithelial cells and red blood cells and higher levels of retained urea nitrogen and non-protein nitrogen in the blood.

BACITRACIN IN AMEBIASIS

During the month of March, 1948, it was reported by Dr. E. C. Faust[11] of Tulane University in New Orleans that he had found Endameba histolytica susceptible to bacitracin, and because of the striking sensitivity of associated intestinal bacteria of the clostridial and coccal groups, plans were formulated for an intensive study of amebiasis.

This study was carried out by Dr. Harry Most of the Department of Preventive Medicine of New York University.[12] The patients were for the most part returned veterans from World War II who had acquired their infestation in widely separated war areas. Treatment was carried out in New York where re-infestation from outside sources was unlikely. Sixty patients were treated all of whom were having active symptoms and signs of amebiasis. The first fifty patients received bacitracin by mouth in amounts ranging from 40,000 to 160,000 units a day in divided doses for a period of twenty days. A careful follow-up of these cases was carried out over a period of six to twelve months. There were no clinical failures but there was a relapse rate of about 30 per cent, as represented by a return of the Endameba histolytica in the stools without any clinical symptoms. These organisms are being studied further to see if they have lost their pathogenicity. Some of the patients with relapses responded to a second series of treatments with a higher dosage. The last ten patients were treated with 160,000 units a day for twenty days. They have not yet been followed long enough to determine the percentage of cures. In all of these patients there were

only two who showed any disturbances from the treatment itself. One of these had a diarrhea for two days and the other a diarrhea for seven days with distention but this did not require cessation of treatment. The drug was only slightly absorbed from the gastrointestinal tract. It was recovered in small quantities in the urine but no blood levels were demonstrable. High concentrations were still present in the stool.

Dr. Alfred Longacre and Dr. D'Antoni obtained similar results in New Orleans.[13] Their problem of follow-up studies was more difficult because of the possibility of re-infestation from outside sources. Doses as large as 250,000 units a day were given without evidence of toxicity.

BACITRACIN IN NEUROLOGIC INFECTIONS

In the spring of 1948, Dr. Paul Teng, working on the problem of staphylococcic meningitis, demonstrated that bacitracin given intramuscularly in normal dogs can be found in only small quantities in the spinal fluid, indicating difficulty in passing the blood-brain barrier. However, if the meninges are inflamed by the injection of staphylococci into the cisterna magna of dogs, bacitracin enters the spinal fluid in considerably higher concentration. He also demonstrated that if meningitis is produced by the cisternal injection of staphylococci, the animals die within four or five hours of an extensive meningitis; but if bacitracin is instilled into the cisterna magna in such cases, they may be saved even when treatment is initiated two or three hours after inoculation with the bacteria. Furthermore, bacitracin may be injected intrathecally in a concentration of 10,000 units per cc. without showing any signs of irritation of the meninges from the drug.[14]

Dr. William Cone in Montreal has recently demonstrated that powdered bacitracin, containing 50 units per mg., may be applied to the surface of the brain without causing the convulsions which are characteristic of the application of penicillin, streptomycin and the sulfonamides. Moreover, it can be injected into the brain tissue or into the ventricles in a concentration of 1,000 units per cc. without causing any evidence of irritation.

BACITRACIN IN THE TREATMENT OF PNEUMONIA

Reisner continued his study of the intramuscular injection of bacitracin in cases of pneumonia until he had a series of twenty-five.[15] In a preliminary group of eleven cases he found that doses as small as 15,000 units every six hours would cause rapid resolution of the process if the organism had not invaded the blood stream, but that higher doses were necessary in the presence of septicemia. In his second series of fourteen cases the initial treatment was usually 30,000 units every six hours, but in several instances of severe and extensive infection he doubled this dose and in one patient gave as much as 99,000 units every six hours. He recommended the use of bacitracin in cases of pneumonia caused by a sensitive organism which did not respond to penicillin. In his second series there was only one death and that patient had already developed endocarditis when treatment with bacitracin began. The patient failed to respond not only to bacitracin but to penicillin as well. One other patient with a relatively resistant organism failed to respond to bacitracin but was quickly restored by large doses of penicillin. In this series of cases evidences of nephrotoxicity were minimal and none of the patients showed any permanent or serious damage to the kidneys.

NEPHROTOXICITY OF SYSTEMIC BACITRACIN

Up until May, 1948, further observations were made with the systemic administration of bacitracin and these provided data in 105 cases of surgical infections which were reported to the American Surgical Association at the meeting in Quebec. In this report the recent appearance of disturbing nephrotoxicity was discussed.[16]

During this period Dr. Alexander Michie at the University of Pennsylvania studied

glomerular and tubular filtration in several patients after the administration of bacitracin in daily doses of 200,000 units for varying numbers of days. He found that both of these excretory functions as well as renal blood flow were temporarily but materially diminished. The renal plasma flow in six patients treated for four to nineteen days was reduced 46 per cent. In these same cases the glomerular filtration was diminished 40 per cent. In five of these patients treated for five to nineteen days the tubular filtration was diminished 61 per cent. These sets of figures, however, did not run parallel with each other nor with the total dosage of the drug. Moreover, later tests showed a return toward normal in every case.[17] These experiments were carried out with two Commercial Solvents' lots of bacitracin and a later review of the clinical results with these lots in all of the centers of observation indicated that they were among the most toxic.

Toward the end of this period more cases showing nephrotoxicity appeared in all of the units which were now beginning to use the Commercial Solvents material made in the deep tanks since most of the surface growth product had been used up. It was then evident that the specifications for toxicity which the Food and Drug Administration had set up were too low and that the problem would require a thorough study.

The summary sheets covering the clinical data from all of the patients previously treated were carefully scrutinized from the point of view of the lot numbers and the dosage used. These items were correlated with the laboratory and clinical evidence of kidney irritation. At the same time six representative lots from both the surface growth and from the deep tank product, all of which had been used clinically, were injected subcutaneously into mice in doses ranging from 250 to 1,000 units. Four hundred eighty-four mice were used in this study. With each lot the death rate was noted and after a period of several days the surviving mice were sacrificed and notes were made with regard to the evidence of gross renal disorders.

When all of the laboratory and clinical data were analyzed, it was obvious that the early deep tank product was definitely more toxic than the surface growth product. Furthermore, it was evident that different lots of the deep tank product differed from one another in their toxicity. These lots had all been tested for safety by the laboratories of the Food and Drug Administration and it was found that the LD-50 for 20-gram mice ranged all the way from 224 to 500 units. It was then found that these F.D.A. tests corresponded very closely with the clinical and laboratory data mentioned above. The lot which met the LD-50 test of 500 units was by far the least toxic in its clinical record in cases of surgical infections and pneumonia.

When faced with the clinical and laboratory data, the deep tank manufacturers suggested that, inasmuch as their product had a higher assay and was therefore purer than the surface growth product, some inhibiting substance which had reduced the toxicity of the surface growth material might have been removed by their process. It had been demonstrated and repeatedly confirmed that the presence of certain salts materially cuts down the toxicity. It was pointed out that certain of the *d*-amino acids were known to have nephrotoxic action. These might be the responsible elements causing toxicity and their action might be nullified by the presence of the *l*-isomers. It was therefore decided to make a thorough study of the amino acid and salt content of a number of different lots produced by the two methods.

Inasmuch as the surface growth material was almost exhausted, we were dependent entirely upon the Commercial Solvents deep tank bacitracin. Fortunately, other lots made fairly recently met the 500-unit specification and these were selected for further clinical trial. It was agreed that initial doses should approximate 200 units per Kg. of body weight and that these doses should be increased only if the initial dose

failed to control the infection under treatment. This plan was followed during the course of the next eleven months and the favorable results obtained with a minimum of disturbing toxic manifestations amply justified this program and has restored confidence in the safety and efficacy of the antibiotic.

In order to be certain that the low incidence of nephrotoxic responses in the patients receiving the bacitracin with the LD-50 of 500 was not simply a question of low dosage, six patients during this period were given the same doses from two lots which fell short of this specification. Four of the six gave disturbing signs of toxicity which disappeared as soon as they were taken off this material and given the same dosage with a less toxic lot. One of these patients had been given some of the surface growth bacitracin a year previously for a period of one month in a dosage 50 per cent higher without any evidence of toxicity.

TABLE 1
ANTIBACTERIAL SPECTRUM OF BACITRACIN

Organisms	*Sensitive to Bacitracin (in units)	*Resistant to Bacitracin (in units)
Aerobic Bacteria:		
β hemolytic streptococci		
Groups A, B, C, F, G	0.025–0.005	
Group D	3–0.008	
Non-hemolytic streptococci	3–0.025	
Pneumococci	0.1–0.002	
Staphylococci (coagulase +)	5–0.05	
Other micrococci	5–0.008	
C. xerose	0.005–0.003	
C. diphtheriae	0.015–0.004	
N. meningitidis	0.01	
N. gonorrhoeae	0.006	
†B. anthracis	4–12.5	
B. subtilis group		50
E. coli		50
A. aerogenes		50
A. cloacae		50
Proteus		50
Ps. aeruginosa		50
B. alkaligenes		50
S. typhosa		50
Sh. alcalescens		50
Flavobacterium (New Orleans strain)	0.0025	
‡H. influenzae Type B	.63	
Anaerobic Bacteria:		
Cl. welchii	0.025–0.002	
Cl. septicum	0.01–0.002	
Cl. sordellii	0.01–0.005	
Cl. novyi	0.01	
Cl. tetani	0.01–0.006	
Cl. histolyticum	0.025–0.004	
Hemolytic streptococci	0.01–0.001	
Non-hemolytic streptococci	0.1–0.005	
Micrococci	0.5–0.005	
Diphtheroids	0.003	
Actinomyces israeli	0.075–0.005	
§T. pallidum (Reiter strain)	0.004	
Fungi:		
Monilia albicans		50
Cryptococcus hominus		50
Nocardia asteroides		50

* Beef heart infusion broth tube assay.
† Occasional strains sensitive 3–0.5 units.
‡ EVANS, F. *J. Bact.*, 56: 507, 1948.
§ EAGLE, H., MUSSELMAN, A. D. and FLEISCHMAN, R. *J. Bact.*, 55: 347, 1948.

THREE PHASES OF CLINICAL EXPERIENCE WITH BACITRACIN

Thus the clinical experience of the various units which were set up for the clinical appraisal of bacitracin over a period of twenty-two months has had three phases: (1) a period of calm and complacency during which satisfactory results were obtained in about eighty-five cases without toxic manifestations, using the surface growth bacitracin; (2) a period of storm, stress and uncertainty while we treated another eighty-five patients with the early deep tank bacitracin and encountered disturbing evidences of kidney irritation or damage from particularly toxic lots and (3) a period of increasing confidence in the efficacy and safety of bacitracin which meets the specification for toxicity of LD-50 of 500 units for a 20-gram mouse. This has covered about a hundred cases, making a total of 270 for the entire series.[18]

FURTHER PURIFICATION STUDIES

In the meanwhile studies have been going on in an effort to purify further the commercial product. Craig, Gregory and Barry[19] have subjected it to their countercurrent distribution apparatus and have been able to take material with an initial potency of 46 units per mg. and separate

from it a single active substance with an assay of 66 units. Hydrolysis of this material in 6 normal hydrochloric acid followed by paper chromatography gave spots corresponding to phenylalanine, leucine, isoleucine, cysteine, valine, histidine, ornithine, lysine and glutamic and aspartic acids. This strongly suggests that the active principle is a polypeptide of considerable size. All of the constituent amino acids indicated by paper chromatography have been isolated in crystalline form with the correct carbon and hydrogen analyses except lysine and ornithine. The amino acids isolated were as follows: *l*-histidine, partially racemic and *l*-leucine, *l*-cysteine and *l*-glutamic acid, *d,l*-phenylalanine, *d,l*-aspartic acid and partially racemic and *d*-isoleucine. One of the purified specimens showed definite organization when examined microscopically.

Further studies in the Biochemistry Laboratory of the College of Physicians and Surgeons by Miss Catherine Phillips under the counsel of Dr. Hans Clarke have been directed toward further purification of the commercial product to minimize still further or to remove, if possible, all toxicity from the active principle. Attempts to purify commercial bacitracin by treatment with sodium chloride indicated that over 96 per cent of the active material could be precipitated. The product showed no improvement in toxicity.

Drs. Goorley and Brown's work[20] on the precipitation of bacitracin with iodine as a means of checking antibiotic activity chemically was repeated. A relatively large batch of bacitracin (Lot No. 481101) was subjected to iodine precipitation. The precipitate was decomposed with an excess of finely divided silver in a medium containing water, acetic acid and methanol. The clear, almost colorless filtrate from this reaction was evaporated to dryness under reduced pressure. The residue (about 75 per cent of original weight) showed unaltered activity but no improvement in toxicity.

Fractional precipitation with picric acid was also carried out on a Commercial Solvents preparation. The antibiotic-picrate was regenerated from the resulting precipitates by treatment with hydrochloric acid and extraction of picric acid with ether. However, since potency was not increased nor toxicity removed, further attempts to purify bacitracin were continued by means of liquid-liquid extractions following the activity with nitrogen and sulfur determinations. The work on the separation of the amino acid components is being continued in the Columbia laboratories as well as further attempts to separate antibiotic and toxic factors from bacitracin produced in industrial laboratories.

STUDIES IN EXPERIMENTAL GAS GANGRENE

Sandusky has continued his excellent experimental studies on gas gangrene in guinea pigs and found that bacitracin was capable of preventing the development of the lesion in all but one of a series of 171 animals injected with *Cl. welchii*, while 109 of 130 controls died of the infection. He had some late deaths in his animals, thought to be due to some toxic effect of the drug, and he confirmed our conclusion that different lots differed significantly in this toxicity.[21]

ANALYSIS OF THE WHOLE CLINICAL SERIES

The clinical results were grouped in four categories. The result was considered to be "excellent" if the response was sudden or dramatic and the infection brought under control within seventy-two hours; "good" if there was a definite response but somewhat slower in its evolution; "questionable" if the observer believed that the case might have done just as well without the drug as with it; and "no effect" when it was obvious that the infection had run its course regardless of the treatment. The over-all results are shown in Table II.

Of the 270 patients in the series so far treated, about three-fifths had failed to respond to other treatment or a combination of treatments and yet 55.6 per cent of these gave a favorable response to bacitracin. If it had not been available, many of these patients would have gone on with

their infections with prolonged illness, permanent or temporary disability or death. These have therefore been called "salvaged cases." One hundred twenty-six of these cases had failed to respond to penicillin alone or to penicillin in combination with other drugs. The three largest groups were "penicillin only" in which there were thirty-seven cases, "penicillin with some sulfonamide" thirty-one, and "penicillin, streptomycin and some sulfonamide" twenty-eight. Of the ninety-six cases in these three main categories of penicillin treatment there were twenty-three which gave a brilliant response to bacitracin and in thirty-two it was called "good"—a total favorable result of 57 per cent.

TABLE II
OVER-ALL RESULTS OF SYSTEMIC BACITRACIN TREATMENT IN 270 CASES ACCORDING TO DIAGNOSIS

Diagnosis	Total Cases	Results of Treatment			
		Excellent	Good	Questionable	No Effect
Cellulitis	31	16	10	2	3
Pneumonia	27	16	2	0	9
Infected accidental wound	20	6	12	1	1
Deep abscess	19	5	10	2	2
Infected operation wound	14	2	5	2	5
Chronic osteomyelitis	12	0	4	4	4
Carbuncle(s)	8	1	6	0	1
Endocarditis	8	0	0	1	7
Prophylactic	7	1	6	0	0
Ulcer(s) of leg(s)	7	0	4	2	1
Undermining burrowing ulcer	6	2	2	0	2
Staphylococcic meningitis	5	5	0	0	0
Synergistic gangrene	5	4	1	0	0
Acute osteomyelitis	4	0	3	0	1
Superficial abscess	4	0	2	1	1
Multiple furuncles	4	0	1	1	2
Ulcerative colitis	4	0	0	2	2
Human bite infection	3	2	0	0	1
Furuncle	3	0	3	0	0
Actinomycosis	3	0	1	2	0
Miscellaneous (2 each)	32	5	13	3	11
Miscellaneous (1 each)	44	5	22	9	8
Totals	270	70	107	32	61
	Favorable results in 65.6% of cases.				

Of the 119 cases that had had no previous antibiotic treatment, the favorable responses to bacitracin were 78.1 per cent. This difference can be largely explained on the basis of earlier treatment in the latter group.

About half of the cases were treated with systemic bacitracin alone and the others with both systemic and local bacitracin. The favorable results in the latter series (75.6 per cent) were considerably better than in the former (56.4 per cent), but these series are not strictly comparable because in the former group the infections were more serious, the inflammation was more diffuse and was often not sufficiently localized to permit local treatment. Moreover, many of these cases did not have the benefit of surgical drainage.

Bacteriologic studies in these cases revealed that the majority were infected with a mixture of organisms. This was especially true in the chronic cases which had lasted for a month or more before treatment with bacitracin began, and yet the response to bacitracin was almost if not just as good in these mixed infections as in the pure infections. This was probably due to the fact that bacitracin has a very wide antibacterial spectrum and is not inhibited as is penicillin by the penicillinase producers which are so frequently present in mixed infections.

Most of the organisms found associated with these infections were tested for their susceptibility to both penicillin and bacitracin. One hundred twenty-two species were susceptible to both, 104 were susceptible to bacitracin but not to penicillin while only eleven were resistant to bacitracin and susceptible to penicillin. Where there was a difference, therefore, the ratio was about 10 to 1 in favor of bacitracin. This ratio is twice as great as appeared in a similar study of patients treated locally with bacitracin two years ago.[4] Furthermore, the ratio is favorable to bacitracin in every bacterial group. This would suggest that as time goes on more and more infections will be found to be due to organisms which are resistant to penicillin and are susceptible to bacitracin.

If this comparison of bacterial susceptibility to bacitracin and penicillin is analyzed further so as to reveal the difference between the group which had been previously treated with systemic penicillin and the group which had not, the ratio of bacitracin to penicillin is found to be 35 to 1 in the

former, while in the latter group the ratio is less than 4 to 1. This is clearly shown in Tables III and IV.

These figures would seem to indicate clearly that many organisms had built up a resistance to penicillin in response to systemic treatment with it. With wider use of bacitracin, resistance to it probably will in turn be gradually built up.

TABLE III

SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED FROM THE LESIONS OF CASES WITH PREVIOUS PENICILLIN TREATMENT

Bacteriology	Bacitracin S. Penicillin S.	Bacitracin S. Penicillin R.	Bacitracin R. Penicillin S.	Bacitracin R. Penicillin R.
Hemolytic strept.	13	9	0	3
Non-hemolytic strept. . . .	6	9	0	1
Coag. pos. staph.	12	27	0	2
Coag. neg. staph.	6	3	1	1
Coag. not tested staph. . .	1	13	1	0
Other aerobic cocci.	3	2	0	1
Anaerobic cocci.	8	3	0	3
Gram-neg. bacilli.	0	2	0	52
Gram-pos. bacilli.	2	3	0	5
Clostridia.	3	0	0	0
Totals.	54	71	2	68

S.—Susceptible
R.—Resistant
Note—Cases with previous treatment unknown are not included.

TABLE IV

SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED FROM THE LESIONS OF CASES WITH NO PREVIOUS PENICILLIN TREATMENT

Bacteriology	Bacitracin S. Penicillin S.	Bacitracin S. Penicillin R.	Bacitracin R. Penicillin S.	Bacitracin R. Penicillin R.
Hemolytic strept.	9	4	1	0
Non-hemolytic strept. . . .	4	3	0	1
Coag. pos. staph.	13	7	2	1
Coag. neg. staph.	4	4	0	0
Coag. unknown staph. . .	12	5	5	0
Other aerobic cocci.	1	1	0	1
Anaerobic cocci.	6	0	0	1
Gram-neg. bacilli.	0	2	0	11
Gram-pos. bacilli.	3	2	0	4
Clostridia.	3	2	0	1
Totals.	55	30	8	20

S.—Susceptible
R.—Resistant
Note—Cases with previous treatment unknown are not included.

In many instances a synergism could be demonstrated between penicillin and bacitracin in the inhibition of bacterial growth. Often one-tenth of the inhibiting dose of one added to one-tenth or one-fifth of the inhibiting dose of the other would completely prevent the growth of the test organisms. In a number of cases there seemed to be clinical confirmation of this synergism *in vivo*. This interesting feature of antibiotic therapy warrants further study and is of great practical value both from the point of view of effecting a higher percentage of cures in the treatment of infections and of making economical use of these materials.

Whether or not bacitracin can be further purified and the toxicity be as completely removed as in the case of penicillin and streptomycin remains to be seen. Nevertheless, the presently available product which meets the specification of LD-50 of 500 units for a 20-gram mouse is sufficiently safe to warrant its widespread use in cases in which the infecting organisms are susceptible to bacitracin and resistant to other antibiotics or which have failed to respond to other methods of treatment.

SUMMARY

1. Bacitracin is an antibiotic produced by a strain of B. subtilis recovered from the débrided tissue removed from a compound fracture. It has a wide antibacterial spectrum and is not inhibited by the penicillinase producers.

2. Bacitracin has been produced commercially and is available as a lyophilized powder which has been accepted by the Food and Drug Administration for local use in the treatment of infections. These

infections have responded favorably in the great majority of cases when the drug was applied locally in the form of a solution or in an ointment base, or when the solution was injected locally into the inflamed tissues or instilled after the aspiration of a purulent exudate from an abscess cavity.

3. Many patients with surgical, dermatologic and ophthalmologic infections have been reported successfully treated in this manner without any evidence of toxicity and with minimal allergenicity.

4. Bacitracin has been found to be lethal for Endameba histolytica and has been effective by oral administration in the treatment of amebiasis. It is not toxic when given by mouth and is not readily absorbed.

5. Bacitracin is retained in the alimentary tract and acts upon many of the intestinal bacterial species.

6. Bacitracin has been administered by intramuscular injection in the systemic treatment of various types of infections in 270 cases, with a favorable response in about two-thirds of the patients. More than half of this series had failed to respond previously to other methods of antibacterial therapy, and more than half of these responded favorably to bacitracin.

7. Some of the patients treat intramuscularly with bacitracin showed disturbing symptoms and signs of kidney irritation but these can be reduced to a minimum if the commercial product can consistently meet a specification of LD-50 of 500 units for a 20-gram mouse.

8. There is evidence that there is a synergistic action between penicillin and bacitracin in the control of infections.

9. Chemical studies are being pursued in an effort to purify this drug further, to identify the active principle and to separate it if possible from the toxic factor so that it may be administered in large quantities as safely as is penicillin.

REFERENCES

1. Johnson, B. A., Anker, H. and Meleney, F. L. Bacitracin: a new antibiotic produced by a member of the B. subtilis group. *Science*, 102: 376–377, 1945.
2. Anker, H. S., Johnson, B. A., Goldberg, J. and Meleney, F. L. Bacitracin: methods of production, concentration and partial purification, with a summary of the chemical properties of crude bacitracin. *J. Bact.*, 55: 249–255, 1948.
3. Scudi, J. V., Coret, I. A. and Antapol, W. Some pharmacological characteristics of bacitracin III. Chronic toxicity studies of commercial bacitracin in the dog and monkey. *Proc. Soc. Exper. Biol. & Med.*, 66: 558–561, 1947.
4. Meleney, F. L. and Johnson, B. A. Bacitracin therapy. The first hundred cases of surgical infections treated locally with the antibiotic. *J. A. M. A.*, 133: 675–680, 1947.
5. Scudi, J. V. and Antapol, W. Some pharmacological characteristics of bacitracin. *Proc. Soc. Exper. Biol. & Med.*, 64: 503–506, 1947.
6. Scudi, J. V., Clift, M. E. and Krueger, R. A. Some pharmacological characteristics of bacitracin II. Absorption and excretion of bacitracin in the dog. *Proc. Soc. Exper. Biol. & Med.*, 65: 9–13, 1947.
7. Bond, G. C., VanderBrook, M. J., Wiley, J. L. and Nook, M. A. Oral administration of bacitracin. *Proc. Soc. Exper. Biol. & Med.*, 68: 395–400, 1948.
8. Eagle, H. and Fleishman, R. Therapeutic activity of bacitracin in rabbit syphilis, and its synergistic action with penicillin. *Proc. Soc. Exper. Biol. & Med.*, 68: 415–417, 1948.
9. Eagle, H. Data to be published.
10. Miller, J. L., Slatkin, M. H. and Johnson, B. A. Local use of bacitracin. *J. Invest. Dermat.*, 10: 179–188, 1948.
11. Faust, E. C. Personal communication.
12. Most, H. Data to be published.
13. Longacre, A. B. Personal communication.
14. Teng, P. and Meleney, F. L. Bacitracin levels in the cerebrospinal fluid after parenteral injections. Bacitracin therapy of experimental staphylococcal meningitis in the dog. Accepted for publication in *Surgery*.
15. Reisner, E. H., Jr., Bailey, F. N. and Applebaum, E. The treatment of pneumonia with bacitracin. *Ann. Int. Med.*, to be published.
16. Meleney, F. L., Altemeier, W. A., Longacre, A. B., Pulaski, E. J. and Zintel, H. A. The results of the systemic administration of the antibiotic, bacitracin, in surgical infections. A preliminary report. *Ann. Surg.*, 128: 714–731, 1948.
17. Michie, A. Personal communication.
18. Meleney, F. L., Longacre, A. B., Altemeier, W. A., Reisner, E. H., Jr., Pulaski, E. J. and Zintel, H. A. The efficacy and the safety of the systemic administration of bacitracin in various types of surgical and certain medical infections with an analysis of 270 cases. *Surg., Gynec. & Obst.*, to be published.
19. Craig, L. C., Gregory, J. D. and Barry, G. T. Purity studies on polypeptide antibiotics: bacitracin. Read before the Second National Symposium on Recent Advances in Antibiotics Research in Washington, D. C., April 12, 1949.
20. Brown, M. Personal communication.
21. Sandusky, W. R., Keeble, E. F. and Wharton, W. P. The use of bacitracin in experimental clostridial infections. Accepted for publication in *Ann. Surg.*

The Polymyxins*

A Review and Assessment

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POLYMYXIN is a generic term for a group of related antibiotics derived from Bacillus polymyxa, a spore-forming rod occurring in soil. The various polymyxins are relatively simple, basic polypeptides which form water-soluble salts with mineral acids. Biologically they are characterized by their high activity against gram-negative bacteria and their therapeutic activity in systemic infections produced by susceptible micro-organisms.

CHEMISTRY

Four distinct polymyxins have been isolated from the metabolism liquor of different strains of B. polymyxa and are designated polymyxins A, B, C and D.[1] Polymyxin A was formerly called "Aerosporin" and polymyxin D "Polymyxin." The peptide nature of the polymyxins, which have molecular weights of at least 1,000, is well-established and their amino acid composition has been determined.[2–4] These are given in Table 1. It can be seen that each of the polymyxins consist of only three or four α-amino acids, and that those common to all are α,γ-diaminobutyric acid and threonine. The isolation of α,γ-diaminobutyric acid from the polymyxins represents the first demonstration of this amino acid as a constituent of a natural product.

The configuration of the amino acids in polymyxins A and D has been established as L (so-called "natural" configuration) for α,γ-diaminobutyric acid and threonine, and D (so-called "unnatural" configuration) for leucine and serine.

In addition to the amino acids shown in Table 1 the polymyxins also contain an optically active branched-chain fatty acid of empirical formula $C_9H_{18}O_2$ which is identical in polymyxins A, B and D. According to Catch et al.[4] the substance is 6-methyloctanoic acid and is thought to exist as an N-acyl group in the polymyxin molecule.

TABLE 1
AMINO ACID COMPOSITION OF THE POLYMYXINS

Polymyxin	α, γ-Diaminobutyric Acid	Threonine	Leucine	Phenylalanine	Serine
A	+	+	+		
B	+	+	+	+	
C	+	+		+	
D	+	+	+		+

+ denotes presence of amino acid.

There is ample evidence from partition chromatography and solvent distribution studies[2] for the elaboration by polymyxin D-producing strains of B. polymyxa of smaller quantities of biologically active components which appear to have the same qualitative and quantitative composition as polymyxin D but differ from it physically and possibly biologically. Jones[3] also describes a polymyxin (polymyxin E) the qualitative composition of which is identical with that of polymyxin A but the speed of which in partition chromatography approximates B.

The polymyxins are stable under physiologic conditions of pH and temperature either in aqueous solution or as a powder. On the other hand, polymyxin D and pre-

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sumably the other polymyxins are unstable under alkaline but not acid conditions, the rate of destruction depending upon the pH and temperature.[5] Polymyxins A and D are unaffected by proteolytic enzymes.[6,7]

The remarks which follow are concerned with polymyxins A, B and D. No experimental investigations have been reported for polymyxins C or E.*

ANTIBACTERIAL ACTIVITY IN VITRO

The outstanding antibiotic property of the polymyxins is their specificity for gram-negative bacteria and, as a corollary, their almost uniform lack of activity against gram-positive bacteria. To those concerned with problems of this nature the polymyxins may provide a useful tool in elucidating fundamental distinctions between these two groups of micro-organisms. Available information indicates[6,8] that polymyxins A, B and D of comparable purity do not differ materially in their effect on bacteria *in vitro* either qualitatively or quantitatively.

As might be expected, refractory organisms in the gram-negative group occur. Members of the genus Proteus are generally resistant although exceptions to this exist.[5] All other genera studied are sensitive. These include Aerobacter, Brucella, Eberthella, Escherichia, Hemophilus, Klebsiella, Pasteurella, Pseudomonas, Salmonella, Shigella and Vibrio. Occasional resistant species or strains are encountered, however, and some variation in sensitivity from genus to genus, species to species and strain to strain have been observed. Some Neisseria have been found sensitive to A and D, others resistant. A peculiar finding[10] is the resistance *in vitro* of a strain of N. intracellularis against which, however, polymyxin D was effective in mice.

The size of inoculum has an appreciable effect on the titration end points of the polymyxins. Thus increasing the inoculum by ten-fold steps from about 2 cells to 20,000,000 cells of E. coli per ml. raised the end point also stepwise from 0.02 to 6 μg./ml. of polymyxin D.[8]

The activity of the polymyxins does not appear to be appreciably affected by the composition or pH of the test medium or by the inclusion of blood or serum.[5,11] Bliss et al.[11] noted moderate antagonism of polymyxin D by soap, lecithin and lipositol.

A notable feature of the polymyxins is the difficulty experienced by most investigators in developing resistant strains from sensitive species.[5,10,12,15] Presumably, therefore, resistant mutants are rare. Nevertheless, resistant strains have been obtained experimentally in some instances.[5,13]

There is general agreement that the polymyxins are rapidly bactericidal and that this is the primary antibiotic action. As an indication of the speed of sterilization, Bliss et al.[11] found that when 100,000 cells per ml. of E. coli were exposed to 0.2 μg./ml. of polymyxin D in broth, only 20 viable cells per ml. remained after one hour and one after three hours.

A phenomenon which may have bearing on the mechanism of action of the polymyxins is the apparent lytic effect on sensitive species by polymyxins A and D noted by White et al.[8] This was evidenced by a rapid decrease in the turbidity of a cell suspension exposed to moderate concentrations of the antibiotics. Heat-killed cells were not affected. Under similar conditions streptomycin failed to cause any change. Not all polymyxin-sensitive strains were "lysed," however. Hence there is no clear cut relation between bactericidal and "lytic" activity.

EXPERIMENTAL CHEMOTHERAPY

The therapeutic effectiveness of polymyxins A, D and, to a lesser extent, B has been determined for a variety of experimental gram-negative infections, particularly in mice. In general, the *in vivo* results parallel the *in vitro* results; that is, infections produced by organisms sensitive to the antibiotic *in vitro* were favorably influenced; infections produced by organisms resistant to the polymyxins *in vitro*, including gram-

* Polymyxin E has been used clinically by Pulaski and Rosenberg.[19] However, E is not treated separately or otherwise distinguished from B in this study.

positive organisms, were unaffected. The one known anomaly in this regard is that previously mentioned concerning a strain of meningococcus.[10]

Experimental chemotherapy has been studied with fewer organisms but in greater detail with polymyxin D[5] than A or B. A typical experiment relating dose to chemotherapeutic effect of polymyxin D in an otherwise rapidly fatal experimental infection with K. pneumoniae in mice is illustrated in Table II and requires no further comment. In agreement with the *in vitro* results, increasing the inoculum increased the dose required to obtain the same therapeutic response. If treatment was delayed after infection, the dose required for a given therapeutic effect was also increased,[14] probably reflecting, in part, the increased number of organisms in the mouse.

A single dose of polymyxin D was found to be more effective than the same amount given in divided doses. Thus in the case of K. pneumoniae in mice[14] a single dose of 1 mg./Kg. at the time of infection protected 85 per cent of the mice; 0.5 mg./Kg. at once followed by 0.5 mg./Kg. at three, six or twenty-five hours protected 70, 65 and 55 per cent, respectively; 0.25 mg./Kg. at once and repeated at three, six and twenty-four hours resulted in only 5 per cent survivors.

Parenterally administered polymyxin D was more effective than orally administered drug. It was found[5] that in the case of K. pneumoniae in mice oral administration required about sixty-four times as much drug to obtain the same therapeutic response as when administration was by the subcutaneous or intravenous route.

Other experimental infections favorably influenced by polymyxin D were Pasteurella multocida,[5,8] H. influenzae b,[14] H. pertussis[8] and E. typhosa in mice,[9] and Shigella gallinarum in fowl.[5]

Experimental mouse infections studied by Brownlee et al.[6,15] and found to be favorably influenced by polymyxin A were E. typhosa, E. coli, H. influenzae, K. pneumoniae, H. bronchisepticus, H. pertussis and Ps. pyocyanea. In the few studies with polymyxin B[6] the results obtained were comparable to polymyxin A.

In direct comparisons of polymyxins A and D of comparable purity White et al.[8] found D to be 30, 50 and 90 per cent as effective as A in experimental infections produced in mice by H. pertussis, K. pneumoniae and P. multocida, respectively. A parallel study by Brownlee et al.[9] with other organisms gave similar results except for H. pertussis, in which case Brownlee considered polymyxin D to be one-seventh as effective as polymyxin A. Both groups of investigators were in agreement that polymyxin D was approximately one-half as acutely toxic for mice as polymyxin A.[6,8]

As was suggested by the *in vitro* results, both polymyxin A[15] and D[10] were found to be about ten times more effective weight for weight than streptomycin in experimental infections in mice produced by susceptible bacteria.

TABLE II*

THERAPEUTIC ACTIVITY OF POLYMYXIN HYDROCHLORIDE AGAINST KLEBSIELLA PNEUMONIAE, STRAIN BE, IN MICE

Mice: Vanderwerken; 16–24 Gm.
Infection: Intraperitoneal; 0.5 cc. of 10^{-5} dilution of a 4-hour broth culture; 5,000 ± 2,000 organisms.
Treatment: Subcutaneous; single dose given immediately after infection; aqueous solutions of drug at pH 7.0 ± 0.2.

Dosage† mg./Kg.	Survival—21 Days after Infection		
	Alive/Total	Per Cent	Time‡
4.0	70/70	100	
2.0	70/70	100	
1.0	70/70	100	
0.8	76/80	95	4.5
0.6	69/80	86	5.6
0.4	40/80	50	3.8
0.2	0/80	0	1.7
Untreated	0/80	0	1.3

* From Polymyxin: a new chemotherapeutic agent. P. G. STANSLY, R. G. SHEPHERD and H. J. WHITE. *Bull. Johns Hopkins Hosp.*, 81: 43–54, 1947. With permission of the Editors.

† Dosage expressed as pure polymyxin hydrochloride, 2,000 units per mg.

‡ Average survival time (days) for mice that died.

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

It should be borne in mind that pharmacologic and clinical data have been obtained with polymyxin preparations of about 70 per cent purity. The impurities may be of minor importance in absorption and distribution of the antibiotics but may play a significant role in producing toxic effects. Unfortunately, the effect of impurities has not been evaluated and we are obliged to consider toxic reactions, whenever they occur, as being due to the antibiotic unless it is proved otherwise.

Lethal Toxicity of Polymyxins A, B and D in Experimental Animals. In mice the acute lethal dose of the polymyxins is dependent upon the route of administration. Thus Brownlee et al.[6] found the relative lethal dose (LD_{50}) for the intravenous, intraperitoneal and subcutaneous routes to be in the approximate order of 1, 2 and 13. This relationship held for each of the antibiotics. With a lethal dose the time at which death occurs is also dependent upon the route of administration, being two to thirty minutes after intravenous, two to four hours after intraperitoneal and up to thirty-six hours after subcutaneous administration for all three antibiotics. For all three routes and for material of equivalent potency, polymyxin D was found to be about one-half as acutely toxic as polymyxins A or B.[6,8] As an indication of the absolute amount of a polymyxin required to produce death the results of Bryer et al.[14] are of interest. They determined the LD_{50} for two lots of polymyxin D administered as a single dose subcutaneously in mice. One lot had an LD_{50} of 250 to 300 mg./Kg. and the other 400 to 500 mg./Kg. The symptoms preceding death were ataxia, convulsions, paralysis and respiratory arrest.

Dogs survived single intravenous injections of 10 to 15 mg./Kg. of polymyxin D. Rapid intravenous injection of 25 mg./Kg. or intravenous drip with a total of 35 mg./Kg. was fatal.[14] The symptoms observed included paralysis and apnea, death occurring at twenty minutes and two and one-half hours, respectively. Doses of 5 or 10 mg./Kg. intramuscularly twice daily for seven days were well tolerated. Intrathecal injections of 1 or 5 mg. produced no untoward reaction while 10 mg. produced a transient paresis of the hind legs.

Experimental and Clinical Absorption, Distribution and Excretion. Therapeutic blood levels are readily attained by parenteral administration of polymyxins A, B and D. Absorption from the gastrointestinal tract also takes place, at least with polymyxins B and D. With adequate dosage therapeutic effects in systemic infections are obtainable by this route both experimentally[5] and clinically.[16]

Polymyxin A: The information available on polymyxin A is meager. Subcutaneously administered in rabbits it appears promptly in the plasma but not in the red cells of the blood nor in the spinal fluid.[15] Swift[17] obtained serum levels of from 0.2 to 1.6 μg./ml. one hour following an intramuscular injection of from 2.1 to 4.0 mg. in children of one month to two and one-half years of age.

Polymyxin B: Polymyxin B was administered by Kaplan et al.[18] to a group of children intramuscularly (0.8 mg./Kg. every four hours for five days) or by aerosol inhalation (0.5 mg./Kg. four times daily for five days). Serum levels determined in twenty-six cases three and one-half to four hours following intramuscular administration gave 2.8 to 7.0 (av. 4.6) μg./ml. Thirteen cases in the aerosol group gave 2.0 to 2.6 (av. 2.3) μg./ml. after one hour. Cumulative effects were not observed since levels were approximately the same on the third, fourth or fifth days of treatment. Ross et al.[16] also found in children that a dosage of 3 mg./Kg. orally every four hours, combined with 0.5 mg./Kg. intramuscularly every four hours, gave spot blood levels of 1.4 to 4.2 μg./ml. No detectable blood level was found upon oral administration alone. It was inferred, however, that absorption took place since one-third of the patients showed elevated blood non-protein nitrogen attributed to the nephrotoxic effect of the drug.

Pulaski and Rosenberg[19] noted that in man the peak serum concentration occurred two hours following intramuscular administration of 2 to 4 mg./Kg. At six hours one-half of the peak concentration was still present, and at twelve hours there was still a measurable level. Cumulative serum concentrations were observed if the doses were more frequent than at twelve-hour intervals. They noted that although excretion of polymyxin B was primarily renal it was slower than that of penicillin or streptomycin. During the first twelve hours after injection less than 0.1 per cent of the dose was recovered in the urine, but following this a progressive increase in urinary excretion occurred. When the daily dose was 3 mg./Kg., the concentration in the urine after twenty-four hours ranged from 40 to 400 μg./ml.

Polymyxin D: In dogs[14] single intramuscular doses of 5 and 10 mg./Kg. gave serum levels of 2.5 and 5.0 μg./ml. after one and one-half hours, decreasing to 1.25 and 2.5 μg./ml. after three and one-half hours. Levels four times these were obtained with similar doses twice daily for seven days. Practically all the antibiotic disappeared from the serum twenty-three hours after the last injection. No polymyxin was detected in the spinal fluid even with serum levels as high as 320 μg./ml. obtained by intravenous drip. Intrathecal administration of 1, 5 and 10 mg. resulted in spinal fluid levels of 10 to 500 μg./ml. which fell to 0.3 to 20 μg./ml. in two to five hours. Blood levels of 1.25 to 0.6 μg./ml. were obtained with the 5 and 10 mg. doses.

In man[20] intramuscular administration of 3 mg./Kg./day in divided three-hourly doses gave blood levels of 0.6 to 1.3 μg./ml. within twelve hours. On continued treatment the level rose to 2.5 and 5 μg./ml. Accumulation of drug was not apparent.

When administered in daily doses of 4 to 7 mg/Kg. a lag in urinary excretion of approximately twelve hours was noted, paralleling the observation made by Pulaski and Rosenberg[19] with polymyxin B. Drug then appeared in the urine, increasing rapidly so that by seventy-two to ninety-six hours approximately 60 per cent of the administered drug was excreted. The concentration in the urine varied between 10 and 100 μg./ml.

Toxic Reactions. Polymyxins A and B: According to Brownlee and Bushby[15] all batches of polymyxin A contained an antidiuretic factor for rats on "high dose" levels. Antidiuresis, however, was not observed in man on "therapeutic" dosage. All batches but one caused damage of the renal tubules which was accompanied by albuminuria. The effect was at first said to vary inversely with purity but subsequent data did not support this conclusion.[6] The antidiuretic and tubule-damaging factors were thought to be distinct.

Brownlee et al.[6] attempted to counteract the tubular effects of polymyxin A in rats by treatment with a variety of amino acids and related compounds. D,L-methionine was considered to be significantly active. In dogs the data indicated that complete protection against the effect of 1 mg. of polymyxin A four times daily was afforded by a single injection of 5 mg./Kg. of methionine. This salutary effect of methionine in counteracting albuminuria caused by polymyxin A did not carry over to man.[6,22]

Comparisons of the renal toxicity of polymyxin A and B were made in the rat, rabbit, dog and, to a minor extent, in man. The protocols, unfortunately, suffer from a lack of clarity. For instance, in the rat experiment the doses administered are not given. In the data on man the two subjects on polymyxin B received one-half and one-fifth, respectively, of the dose the subjects on polymyxin A received. Furthermore, in several instances an element of uncertainty exists as to whether or not the dose was adjusted in accordance with the varying potencies of the batches of drug used. The rabbit and dog experiments were less confusing and the data in these suggest that less proteinuria was associated with administration of polymyxin B than A.

In man the most serious symptoms associ-

ated with administration of the polymyxins are those attributable to renal damage. Of lesser importance are certain subjective nervous symptoms associated with administration of polymyxin B and, possibly, of E. Finally, minor disturbances, such as elevated temperatures, malaise, etc., have also occurred with the various polymyxins.

Ross et al.[16] treated patients orally with polymyxin B, or both orally (2 to 3 mg./Kg. every four hours) and intramuscularly (0.5 mg./Kg. every four hours). Only six cases comprised the latter group. The majority of toxic reactions occurred after intramuscular administration. Malaise and anorexia were noted in three of the six patients. Blood non-protein nitrogen did not increase significantly. Albuminuria, ranging from 15 to 200 mg. per cent, was observed in two of the six cases while casts and white cells were seen in five. In all instances urinary and blood abnormalities disappeared within two to four days after termination of therapy.

Pulaski and Rosenberg[19] studied twenty cases of severe urinary tract infections treated with polymyxins B or E. Treatment was intramuscular for two to six days. None of the patients developed drug sensitivity. When the dosage did not exceed 2.5 mg./Kg./day, there was no increase in blood urea, blood non-protein nitrogen or any consistent evidence of nephrotoxicity. When the dosage exceeded 4 mg./Kg., the amount of albumin and the number of red, white and renal cells in the urine increased. Granular casts were seen only inconstantly. Oliguria and fixation of the specific gravity of the urine at a low level were not consistently observed. In any case urinary abnormalities produced as a result of therapy disappeared within a week after the drug was withdrawn.

In practically every instance, however, nervous phenomena were associated with administration of these two polymyxins. These symptoms consisted of paresthesias and hypesthesias about the face and scalp, mild dizziness and weakness. The symptoms persisted throughout treatment and disappeared within twenty-four hours after completion of therapy. The symptoms were not severe enough to warrant cessation of therapy. Adrenalin, intravenous calcium or antihistaminics did not produce relief. Objective neurologic abnormalities could not be demonstrated.

Jawetz and Coleman[13] also call attention to the neurologic disturbances accompanying therapy with polymyxin B. They lasted while the drug was administered and subsided thirty-six to forty-eight hours after it was discontinued. No residual effects were observed. In their series of ten adults treated intramuscularly with doses of 20 mg. (about 0.5 to 1.0 mg./Kg.) every four to eight hours for three to four days no evidence of renal damage was detected.

In Kaplan's et al.[18] series of eighty-four children treated intramuscularly (0.8 mg./Kg. every four hours for five days) or by inhalation (about 0.5 mg./Kg. four times daily) with polymyxin B, albuminuria was present in thirty-three of sixty-six intramuscularly treated patients, varying from a trace to 3 plus and frequently associated with white cells. In all cases the urinary findings disappeared after treatment was discontinued. The most distressing symptoms noted were marked lethargy, irritability and anorexia in all intramuscularly treated patients. These symptoms persisted until therapy was ended. Oliguria was present in several patients but was believed to be secondary to anorexia. As might be expected, toxicity was less pronounced with aerosol-treated patients because of the lower blood levels obtained.

The only available information concerning polymyxin A is that of Swift[17] who treated ten children intramuscularly with 2.1 to 4.0 mg. (about 0.5 mg./Kg.) of polymyxin A usually at four-hour intervals for varying periods up to seven days. Transient albuminuria developed in nine of the ten patients varying from a trace to 400 mg. per cent. In most instances the albuminuria disappeared within a week. Gross hematuria was not observed but red blood cells and granular and hyaline casts were noted in four of the cases.

Polymyxin D: Experimentally Bryer et al.[14] found that a large single daily subcutaneous dose (20 mg./Kg.) of polymyxin D in dogs led within twenty-four hours of the first injection to the appearance of epithelial cells, cellular casts and albumin in the urine. The specific gravity decreased but the urinary output was maintained and usually increased. The administration of D,L-methionine did not prevent the urinary changes. The albuminuria tended to decrease despite continuation of treatment.

Schoenbach et al.[20] treated twenty-two patients suffering from a variety of infections with polymyxin D intramuscularly (in one case subcutaneously) with 3 to 7 mg./Kg./day in divided doses. Albuminuria, cellular casts, granular casts and large epithelial cells appeared in some of the patients, particularly in those receiving the larger doses. The more severe effects occurred in those patients with pre-existing renal impairment. In some patients the albuminuria disappeared even though treatment continued. Azotemia was noted in four patients and oliguria in one. Epigastric distress with anorexia was noted on five occasions with four patients but disappeared during treatment. Blood counts and liver function tests were normal.

General: Practically all who have studied the polymyxins clinically report an occasional rise in temperature associated with parenteral administration. On the other hand, Kaplan et al.[18] found that sixty-two of sixty-four patients on polymyxin B reacted in this way and developed an average temperature of 101° to 102°F. for as long as therapy was continued.

Pain at the site of intramuscular injection was another frequent complaint, and was relieved in most instances by administration of the drug in 1 per cent procaine or similar anesthetic. According to Kaplan et al. less pain was associated with polymyxin B sulfate than hydrochloride.

Both Brownlee et al.[6] and Bryer et al.[14] are in agreement that the renal damage produced by the polymyxins is confined to the tubular epithelium. The effect on the tubular epithelium is reversible, as evidenced by the fact that (1) clinically the proteinuria disappears upon cessation of drug and sometimes decreases even upon continuation of the drug and (2) experimentally there is histologic evidence of tubule regeneration in animals sacrificed while under continuous administration.[14]

THERAPY IN MAN

Polymyxin A in Pertussis. Swift's series of ten unselected cases of pertussis is the only report available of the therapeutic use of polymyxin A in man.[17] Diagnosis of pertussis was symptomatic except for one case in which the causal organism was isolated. The patients ranged from one month to two and one-half years old. Administration was 0.4 mg. every 4 hours intramuscularly for 5 days in mild infections, and 0.8 mg. every 3 or 4 hours in severe infections. Blood levels at 4 hours were 0.2 to 0.4 μg./ml.

Two cases (fourteen months and two and one-half years) were early and mild and their recovery was uneventful. Three (two months, six and one-half months and two years) were moderately severe and were considered to be favorably influenced by therapy; paroxysms and vomiting rapidly subsided and whooping ceased between the sixth and thirteenth days. The other five patients (one, one and three-fourths, three, five and seventeen months) were severely ill. In two of these death seemed imminent but one (one month) responded promptly and recovered. The other (seven weeks) was complicated by gastroenteritis. Cyanosis, apnea and whooping rapidly disappeared but the child died of gastroenteritis. The third (three months) responded to a second course of polymyxin A but not to the first. The dose of the first course was believed to be too small. The fourth severe case (five months) recovered rapidly and the fifth (seventeen months), a case of two weeks' duration, was responsive but died of staphylococcal lung abscesses.

Swift concluded that "all these cases showed a definite response in the first forty-

eight hours; the ultimate benefit obtained seemed to depend on the duration of symptoms before the start of treatment rather than on the severity of the disease or the patient's age."

Polymyxin A in Abdominal Surgery. Polymyxin A was included by Pulaski et al.[21] in a study to evaluate various substances as preoperative antiseptics in gastrointestinal surgery. Twelve patients received 200 or 400 mg. of polymyxin A in divided doses four times daily for as long as sixteen days. All coliform organisms except Proteus were suppressed within twenty-four to sixty hours and suppression was maintained for two days after administration was discontinued. There were no toxic reactions.

Polymyxin B in Specific and Non-Specific Enteritis in Children. Forty patients were treated by Ross et al.[16] as follows: eighteen cases of non-specific enteritis, 2 mg./Kg. orally every four hours for four to ten days; sixteen cases of Shigella enteritis (sonnei and flexner), 3 mg./Kg. orally every four hours for seven to fifteen days; four cases of Salmonella enteritis, orally (3 mg./Kg.) and intramuscularly (0.5 mg./Kg.) every four hours; and two cases of typhoid fever orally (2 mg./Kg.) and intramuscularly (0.5 mg./Kg.) every four hours.

No salutary effect either with respect to the duration or severity of the diarrhea was detected in the patients with non-specific enteritis. The authors note that these results are at variance with the favorable results reported in the majority of some forty odd cases of presumably non-specific gastroenteritis mentioned by Brownlee.[22]

Of the sixteen cases of Shigella infections fourteen were regarded as having been bacteriologically and clinically cured. The stools became negative for the pathogen in one to four days. Only two of the four cases of Salmonella infection received drug long enough to evaluate its effect. One of these was bacteriologically cured while the other suffered a recurrence after cessation of therapy. Therapy in the other two cases was stopped prematurely on account of the appearance of untoward reactions. No striking clinical effect resulted in the two cases of typhoid although the organisms were very sensitive *in vitro* and the bacteriologic response of the patients was regarded as encouraging.

Polymyxin B in Urinary Tract Infections. Twenty patients with severe urinary tract infection were treated with polymyxin B and E by Pulaski and Rosenberg.[19] All but one of these patients had had previous extended trials with other agents including penicillin, streptomycin and sulfonamides. Polymyxin therapy consisted of intramuscular administration of an average of 2.5 mg./Kg./day generally in four divided doses for periods ranging from two to six days.

Ten of the twenty patients were regarded unequivocally as having been benefited by polymyxin. Improvement was noted by the second day of treatment and was manifested by reduction or elimination of bacteria in the urine, regression of symptoms, decrease in fever and improvement in the urine as determined by complete urinary analysis. The outcome was considered to be particularly gratifying in acute Pseudomonas pyelonephritis cases. In all improved patients improvement was sustained for a minimum follow-up of three weeks.

In seven instances the results of polymyxin therapy were considered doubtful. Each of these patients had severe, long-standing pyelonephritis. All the patients, however, had an immediate clinical or bacteriologic response or both but there was either no permanent improvement despite elimination of the organisms or the organisms were not completely eliminated.

Three cases were regarded as failures. One had a Proteus organism resistant to polymyxin. The other two had scarred kidneys with multiple cortical foci of infection. One of the latter patients had in addition a mixed infection, one of the organisms being Proteus.

Jawetz and Coleman[13] studied ten cases of urinary tract infection treated with polymyxin B. All had failed to respond to sulfonamides and streptomycin. Administration of polymyxin was intramuscular,

20 mg. every four to eight hours (approximately 0.5 to 1.0 mg./Kg./day) for three or four days. An effort was made to maintain serum levels between 2 and 10 μg /ml. No detailed analysis of the results are given except in one case. The authors summarize their findings as follows: ". . . Polymyxin B . . . eliminated susceptible bacteria from urine and controlled symptoms. The short course of treatment, however, was followed by a bacteriologic relapse within one to three weeks." The authors regard the therapy as having been, "within its scope, . . . successful." Prolonged treatment was not attempted because of unfavorable side reactions.

Polymyxin B in Influenzal Meningitis. A single case treated successfully with polymyxin B is given in detail by Kagan.[23] The patient was a thirteen month infant who had received large doses of sulfadiazine and streptomycin and also specific rabbit anti-influenzal serum to no avail. When the child had had meningitis for four weeks and a fatal termination seemed inevitable, therapy with polymyxin B was instituted. Administration was intramuscular and intrathecal on the first day (5 mg./Kg. in divided doses intramuscularly and 1 mg. intrathecally) and intrathecal only on the succeeding five days (3.5 mg./day). The infant was afebrile for the first time on the fifth day and markedly improved on the sixth. He improved rapidly and was discharged as cured fifteen days after inception of polymyxin therapy. The causal organism was sensitive to 0.4 units of polymyxin B per ml. A detailed examination of the infant three months after discharge revealed no abnormalities.

Polymyxin B in Pertussis. Kaplan et al.[18] studied the effect of polymyxin B on eighty-four infants and children. Administration in sixty-six patients was intramuscular, 0.8 mg./Kg. every four hours for five days, and in the remainder by aerosol inhalation, about 3 mg./Kg./day in divided doses four times daily. In both series of patients blood levels were well above those necessary to prevent the growth of H. pertussis *in vitro*. Of the sixty-six intramuscularly treated patients twenty-three were adjudged as improved, seven as equivocal and thirty-six as failures. A case was considered as improved if clinical improvement took place within seven days of the start of therapy. Of the patients treated by inhalation five were improved, five equivocal and eight failures.

It was concluded that a significant therapeutic effect of polymyxin B in Pertussis was not clearly demonstrated. It seems unfortunate that the duration of illness before the start of therapy was not taken into consideration in this study. It may be recalled that it was Swift's impression that the efficacy of polymyxin A in pertussis was dependent upon the duration of symptoms prior to institution of therapy.

Polymyxin B in the Local Treatment of Wounds. Pulaski and Rosenberg[19] record that topical application of 1 per cent polymyxin in saline or carbowax resulted in sterilization of several Pseudomonas aeruginosa-infected granulating wounds.

Schoenbach et al.[20] treated twenty-two patients with polymyxin D who suffered with infections produced by a variety of gram-negative organisms. The results are summarized in Table III and those of special interest are amplified below.

Polymyxin D in Pseudomonas Aeruginosa. A case of particular interest was a nine year old boy with generalized exfoliative dermatitis which became infected with Ps. aeruginosa and β Str. hemolyticus. He also had a pyelonephritis with Ps. aeruginosa as the infecting organism. He was considered to be gravely ill and did not improve despite large doses of penicillin, streptomycin and sulfadiazine. Polymyxin therapy was instituted on the twentieth hospital day at a dosage of 3 mg./Kg./day intramuscularly for twenty days. Blood levels of 0.6 to 2.5 μg./ml. were obtained. Cultures of the urine became negative within twenty-four hours and Ps. aeruginosa was completely eliminated from the skin in ten days. Urine examination revealed a 4+ albuminuria and casts on the third day *which disappeared while treatment was continued.* Blood non-

protein nitrogen was 37 mg. per cent before therapy with polymyxin and was unchanged after twenty days of treatment. Because of the streptococcus, penicillin therapy was continued along with polymyxin. The patient completely recovered.

uneventful convalescence after three days of polymyxin therapy.

Polymyxin D in Brucellosis. Two patients with acute brucellosis were treated for ten to fourteen days. Both experienced relief of symptoms rapidly and became afebrile

TABLE III*

SUMMARY OF CLINICAL TRIALS WITH POLYMYXIN D

Disease	No. Treated	Age of Patients	Treatment		Results	
			Daily Dose mg./Kg.	No. of Days	Cultural	Clinical
Pseudomonas aeruginosa infection	3	8 wk.–9 yr.	3–7	3–20	Excellent	Excellent
Pertussis	5	6 wk.–4 yr.	3–7	4–5	Doubtful	Good
Peritonitis†	1	Adult	3	3	.....	Good
Aerobacter aerogenes	3	Adults	4–7	4	Excellent	Good
K. pneumoniae	2	Adults	3–4	4–15	Excellent	Good
Brucellosis	4	Adults	3–7	10–20	Good	Good, acute; chronic, none
Typhoid	4	11, 16, 27, 62 years	4	2–5	Good	Variable

* From The clinical use of polymyxin. E. B. SCHOENBACH, M. S. BRYER and P. H. LONG. *Ann. New York Acad. Sc.*, 51: 987–997, 1949. With permission of the Editors.

† Etiology unknown.

Another case concerned a very severely burned child. The burned areas became infected with Ps. aeruginosa and the child was gravely ill. Polymyxin was administered intramuscularly at a dose of 3 mg./Kg./day for twelve days. The child became afebrile, the exudate cleared and the cultures became negative. There were no complications and convalescence was uneventful.

Polymyxin D in Pertussis. This study involved five cases. It was the opinion of the investigators that the children under one year appeared to benefit from therapy whereas the older age group was more difficult to appraise.

Polymyxin D in Aerobacter Aerogenes. In two cases blood cultures became negative within twenty-four hours after start of therapy and the patients became afebrile.

Polymyxin D in Peritonitis of Unknown Etiology. One patient with peritonitis secondary to a perforated appendix made an within three to four days. Both were asymptomatic on follow-up several months later. No untoward reactions were noted as a result of therapy except transitory albuminuria in one.

Polymyxin D in Typhoid. The variability noted in Table III was due to many complicating factors in the three cases studied. One patient was treated in the fourth week of illness when he was in circulatory shock, distended and delirious. He died sixty hours after treatment was instituted. A second patient responded well to minimal doses of polymyxin (which was scarce at the time) but relapsed three weeks after polymyxin was discontinued. A third case was extremely serious and concerned a sixty-two year old man with pneumonia, phlebitis, prostatic obstruction and high fever. No improvement resulted from treatment with penicillin or streptomycin. Blood and stool cultures were found to be positive for E.

typhosa. Polymyxin in doses of 4 mg./Kg./day was given intramuscularly for five days. The temperature fell within twenty-four hours and was normal on the fifth day of treatment. Blood and stool cultures became negative and the patient made an uneventful recovery after surgical treatment to relieve the prostatic obstruction.

COMMENTS AND CONCLUSIONS

There can be little doubt that the polymyxins have exhibited effective therapeutic activity in certain infections of man produced by gram-negative bacteria. It is apparent, however, that their application in this field is likely to be limited because of the occurrence of untoward reactions elicited by material used in the clinical trials. They will be limited, for instance, to local therapy, to preoperative preparation in abdominal surgery and to those systemic infections in which the dangers of the disease outweigh those of temporary renal damage. The latter would include infections refractory to the sulfonamides, streptomycin or other therapeutic agents, the causal organisms of which are of the type susceptible to the polymyxins. In these instances the polymyxins may, in the words of Long,[24] be life-saving. In other instances, as in infections produced by the Pseudomonas group, the polymyxins may, even in their present state of purity, be the drugs of choice.

The toxic reactions elicited by the relatively crude polymyxins which have been used clinically should certainly not be minimized. On the other hand, it is equally important not to overemphasize their occurrence and seriousness. The renal effects, which have received major attention, were elicited inconstantly and in every case appeared to be transitory, sometimes disappearing even upon continued administration. Whether the subjective nervous symptoms associated with administration of polymyxin B are limited to this particular polymyxin is not known. Here, too, however, the effects were transitory. No permanent injury resulting from administration of the polymyxins in man has yet been reported.

Clinically the fundamental relations of dosage, blood levels, toxicity and therapeutic efficiency have yet to be elucidated, and the scope of the polymyxins in the treatment of infectious diseases determined. It is obvious that much is to be gained if attention is given to supplying qualified investigators with material of increased purity.

In this reviewer's opinion the superiority of one polymyxin over another cannot be considered to have been demonstrated. They do not appear to differ from each other materially in their antibacterial properties. The claim has been made that nephrotoxicity is less frequent and intense with polymyxin B than A or D in experimental animals and is absent in man.[6] The former observation awaits confirmation and the latter is refuted by clinical experience reported in this review. Ultimately, careful clinical comparisons will be necessary should it develop that the polymyxin type of antibiotic finds a useful place in the therapy of infectious diseases caused by gram-negative bacteria.

REFERENCES

1. Stansly, P. G. and Brownlee, G. Nomenclature of polymyxin antibiotics. *Nature*, 163; 611, 1949.
2. Bell, P. H., Bone, J. F., English, J. P., Fellows, C. E., Howard, K. S., Rogers, M. M., Shepherd, R. G. and Winterbottom, R. Chemical studies on polymyxin: comparison with "aerosporin." *Ann. New York Acad. Sc.*, 51; 897–908, 1949.
3. Jones, T. S. G. Chemical evidence for the multiplicity of the antibiotics produced by Bacillus polymyxa. *Ann. New York Acad. Sc.*, 51: 909–916, 1949.
4. Catch, J. R., Jones, T. S. G. and Wilkinson. S. The chemistry of polymyxin A. *Ann. New York Acad. Sc.*, 51: 917–923, 1949.
5. Stansly, P. G., Shepherd, R. G. and White, H. J. Polymyxin: a new chemotherapeutic agent. *Bull. Johns Hopkins Hosp.*, 81: 43–54, 1947.
6. Brownlee, G., Bushby, S. R. M. and Short, E. I. The pharmacology of polymyxin A, B and D. *Ann. New York Acad. Sc.*, 51: 952–967, 1949.
7. Stansly, P. G. and Ananenko, N. H. Resistance of polymyxin to some proteolytic enzymes. *Arch. Biochem.*, 15: 473–474, 1947.
8. White, H. J., Alverson, C. M., Baker, M. J. and Jackson, E. R. Comparative biological studies of polymyxin and "aerosporin." *Ann. New York Acad. Sc.*, 51: 879–890, 1949.

9. Brownlee, G., Bushby, S. R. M. and Short, E. I. Comparative biological studies of polymyxin A and polymyxin D. *Ann. New York Acad. Sc.*, 51: 891–896, 1949.
10. Schoenbach, E. B., Bryer, M. S., Bliss, E. A. and Long, P. H. Polymyxin—a note on experimental and clinical investigation. *J. A. M. A.*, 136: 1096–1098, 1948.
11. Bliss, E. A., Chandler, C. A. and Schoenbach, E. B. *In vitro* studies of polymyxin. *Ann. New York Acad. Sc.*, 51: 944–951, 1949.
12. Ainsworth, G. C., Brown, A. M. and Brownlee, G. "Aerosporin," an antibiotic produced by Bacillus aerosporus Greer. *Nature*, 160: 263, 1947.
13. Jawetz, E. and Coleman, A. B. Laboratory and clinical observations on aerosporin (polymyxin B). *J. Lab. & Clin. Med.*, 34: 751–760, 1949.
14. Bryer, M. S., Schoenbach, E. B. and Bliss, E. A. Pharmacology of polymyxin. *Ann. New York Acad. Sc.*, 51: 935–943, 1949.
15. Brownlee, G. and Bushby, S. R. M. Chemotherapy and pharmacology of aerosporin. *Lancet*, 254: 127, 1948.
16. Ross, S., Burke, F. C., Rice, E. C., Bischoff, H. and Washington, J. A. The use of aerosporin (polymyxin B) in specific and non-specific enteritis in infants and children. *M. Ann. District of Columbia*, 18: 441–503, 1949.
17. Swift, P. N. Treatment of pertussis with aerosporin. *Lancet*, 254: 133, 1948.
18. Kaplan, S., Fischer, A. E. and Kohn, J. L. Treatment of pertussis with polymyxin B. *J. Pediat.*, 35: 49–58, 1949.
19. Pulaski, E. J. and Rosenberg, M. L. Use of polymyxin in gram-negative urinary tract infections. *J. Urol.*, (in press).
20. Schoenbach, E. B., Bryer, M. S. and Long, P. H. The clinical use of polymyxin. *Ann. New York Acad. Sc.*, 51: 987–997, 1949.
21. Pulaski, E. J., Connell, J. F., Jr. and Seeley, S. F. Sterilization of the intestinal tract by antibiotics and supplemental agents. To be published.
22. Brownlee, G. Remarks on clinical results with polymyxin A and B. *Ann. New York Acad. Sc.*, 51: 998–1000, 1949.
23. Kagen, B. M. Influenzal meningitis, recovery of a case of four weeks' duration with the use of a new drug, polymyxin B (aerosporin). *Pediatrics*. 4: 319–322, 1949.
24. Long, P. H., Schoenbach, E. B., Bliss, E. A., Bryer, M. S. and Chandler, C. A. The experimental and clinical use of polymyxin, chloromycetin and aureomycin. *California Med.*, 70: 1–10, 1949.

Clinic on Psychosomatic Problems

Anorexia Nervosa

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. JOHN C. NEMIAH: D. M. (No. 628973), a twenty year old single woman, was brought to the Massachusetts General Hospital from her rooming house in a semi-intoxicated state after the ingestion of an overdose of phenobarbital. Despite a lifetime of maladjusted behavior it was not until nine months before admission that she had first come under medical surveillance. At that time following an argument with her mother, she had taken about a dozen aspirin tablets with suicidal intent. She had been persuaded to consult a psychiatrist but her visits had been irregular and four weeks later she swallowed twelve "empirin" tablets in a second attempt at suicide. After that she ran away from home. For a week she hid in a rooming house, drinking heavily, then returned to her family. She then quit college, lived by herself and managed to work for a few weeks before impulsively leaving her job. From then on she led an aimless life of job-hunting and drinking (with sporadic psychiatric interviews) until she made a third unsuccessful suicidal attempt with phenobarbital four weeks before admission. Another month of similar behavior led to the episode that brought her to the hospital.

There was no family history of psychosis. However, the mother was a fat, immature, self-pitying woman who flew into rages and endlessly scolded and argued with the patient. The father was a small man, quiet, submissive and a hard worker. The patient's only sibling, an older sister, was tense and nervous and was married to an alcoholic law student who worked as a jazz musician by night.

Her past medical history was significant only in that at the age of five years and again at seven the patient had been knocked unconscious for brief periods, each time without known sequellae. The patient had not been a welcome addition to the family. Her mother had made futile attempts at abortion, and the patient's birth had been by cesarean section, allegedly to relieve the mother's anxieties about parturition. The mother had been unable to nurse the baby.

There had been no early childhood habit disorders other than rare enuresis. The patient's first memories reached back to the age of four years. She recalled at that time having tasted her own feces. She had immediately become panic-stricken and had been nauseated for three days. In the same year she had been caught examining a little boy's genitals and had been punished for her curiosity. At the age of five she had felt rejected by her father who once spanked her for wetting her pants; and shortly thereafter when she came into the bathroom and voided in his presence, he had become angry and chased her from the room, telling her that she was now a grown-up girl and must not do such things. After that when she wet her bed she was conscious of shame lest her father discover it.

From six to nine years of age the patient fussed with her food at meals, often throwing it out of the window rather than yield to parental demands to eat. She ran away from home several times, "played hookey" from school, developed a fiery temper and tended to withdraw from other children, preferring to play alone. At the age of ten she remembered believing that impregnation occurred by oral mixing of male and

female saliva and when shortly thereafter she learned the true facts about conception she was shocked, disgusted and upset at the thought of her parents indulging in such activities. At thirteen she first went on a diet lest she become fat like her mother. She was, at this period, a vigorous "tom boy" and had a fear of developing large breasts or looking pregnant.

Her menstrual periods which had begun when she was twelve continued with no disturbance other than mild dysmenorrhea until, at the age of fifteen, she became almost totally anorexic for several weeks and ceased menstruating. (Her periods returned after several months but have been irregular thereafter.) She lost fifteen pounds but noticed no weakness. On the contrary there was an increase in her energy and physical activity. This constellation of symptoms ended abruptly when after being disappointed by a boy she overate one day and promptly vomited. During the next two years there were several such episodes of anorexia followed by the compulsion to overeat followed by vomiting, either spontaneous or induced by tickling her throat. This sequence of gorging and vomiting became so frequent that she referred to it as "the habit." Although ashamed of the procedure, she found that it relieved feelings of depression and disappointment. During this period she ran away from a girl's boarding school where she believed herself disliked by her classmates even though she had been elected class president.

She became aware at this time of a recurrent pattern which had affected her relations with people over many years. Shortly after forming friendships she would begin to feel that her friends were disgusted by her; she would withdraw from them and purposely behave in a way to make them dislike her. She stated her feelings as: "I would rather be hated than be an object of disgust."

When eighteen years of age the patient began college. A long period of anorexia resulted in a loss of weight to 87 pounds but the patient felt so well that she was able to continue a very active life despite frequent parties, little sleep and increasing alcoholic intake. During her second year of college she found herself less satisfied with her friends and began to resort to large doses of benzedrine to stimulate the energy which late hours, great excess of alcohol and rare marijuana smoking tended to dissipate. "The habit" became a prominent symptom, frequently occurring as often as several times a day. She began to cut classes regularly, worried a good deal whether she had had sexual intercourse while drunk and became increasingly discouraged with her life and her behavior. In this wise she continued until the suicidal attempts that preceded hospitalization.

Physical examination revealed the patient to be a small, childish looking girl who was quite thin but not emaciated. No abnormalities were found upon general physical and neurologic examinations.

Laboratory data were as follows: Urinalysis, complete blood count, chest x-ray and skull x-rays were all normal. The blood Hinton test was negative. B.M.R. was minus 11. The electroencephalogram revealed a focus of slow waves in the right occipital region, and when repeated later there were slow waves in the left frontal and left occipital areas. The records were considered abnormal but contained no specific diagnostic features.

In the ward she has been at all times cooperative with the staff and has complied with the hospital rules. There have been rapid alternations of mood: within an hour or a day she may swing from a state of tearful depression to alertness and activity, at times being overenthusiastic and almost abnormally cheerful. Her compulsive stuffing of food and vomiting ("the habit") has continued, especially when she has been depressed.

In the seven weeks since admission the patient has produced an abundance of memories and associations so that the material has of necessity been very much condensed in the presentation. She has reported numerous dreams, one of which

will be mentioned because it so clearly reveals an unconscious fantasy. In the dream the patient was explaining sex to her sister and drew a diagram to illustrate. Within the outline of a human body, she drew "an ovary" (in the region occupied by the stomach) connected above to the esophagus and below to the intestines. A long penis was drawn, hanging from the part of the "ovary" adjacent to the pyloric valve. Inside the "ovary" she sketched a curled-up fetus. In explaining the dream she said that the penis discharged urine with sperm which then crept through the wall of the "ovary" in its lower portion. She corrected herself, saying: "No, it was the *upper* portion." She then said she didn't know why it seemed more natural that the sperm should enter through the upper part. Finally spontaneously she burst out: "You want me to say that the sperm went down through the esophagus."

At presentation of the patient before the group she appeared somewhat tense and was less communicative than usual although poised. When asked how she felt she replied: "A bit cautious."

DISCUSSION

DR. STANLEY COBB: This is a rather abnormal looking electroencephalogram. If she had had numerous fainting attacks or anything related to seizures, we would say the electroencephalogram was significant. It is just as abnormal as those of a lot of epileptics between attacks.

A Rorschach test would be of interest. I was interested in this case because it is said that patients with anorexia nervosa have fantasies of oral impregnation. This she has had, but I wanted to learn if suggestions of this idea by a psychiatrist could be completely ruled out. Dr. Nemiah has been careful about that and is sure that the material showed up spontaneously. So here we have evidence that seems authentic. She has said it in her own words.

For this patient a weight of 83 pounds is not very low. She is very small. She has not reached the extremes of emaciation that some of these patients do. She has had amenorrhea in the past but recently has menstruated. The amenorrhea is usually secondary to the starvation but not always. There are some cases in which it begins before marked weight loss.

DR. JACOB E. FINESINGER: Should one be concerned with the differential diagnosis between Simmonds' disease and anorexia nervosa?

DR. COBB: At present this patient shows no endocrine disturbance. There is a history of amenorrhea. One can almost rule out pituitary disease by the history. Simmond's disease is more progressive, not so much up and down. The history is remarkably interesting, not entirely typical of anorexia nervosa; there are so many extraneous things such as several suicidal attempts, short periods of depression, alcohol which she has used rather excessively and benzedrine. I do not remember another such patient who has used alcohol and benzedrine; they often have a great drive on their starvation sprees and need no stimulant.

DR. FINESINGER: Do you remember another patient with anorexia nervosa who attempted suicide?

DR. COBB: I do not remember one who used drugs to do so. You can look on the whole episode as a suicidal attempt. I do not remember a history that showed such manic-depressive trends.

DR. HENRY H. W. MILES: Is it usual for these patients to show alternating periods of overeating and fasting?

DR. COBB: About 30 per cent of those we have observed have had starvation periods alternating with overeating periods, usually longer than those of this girl. With her, everything is short and episodic. In ordinary cases of anorexia nervosa they starve for months or years and then in the next year will overeat and go up in weight.

DR. VERNON WILLIAMS: Did she tell you why she wanted to do away with herself?

DR. NEMIAH: Her main reason is that she considers herself a "fake," she is no good, there is no point in going on with living.

She is disgusted after an episode of overeating. She had not recognized the starvation as abnormal.

DR. COBB: It is of interest that she uses the word *disgust* which means "bad taste." At the age of ten she had the fantasy about oral impregnation. She wondered about saliva and semen. This is not rare in adolescent girls. Then in the first episode when she stopped eating, it was evidently with the idea that she did not want to be fat and sexy and would rather be like a boy.

DR. NEMIAH: She wanted to avoid secondary sex characteristics and reduce her abdomen which looked pregnant. She did not want to become fat. Her bust and hips were too big. She emphasized that she always used the word "bust" instead of "breast." The latter word she hated.

DR. LUCIE JESSNER: This is a most interesting history and I am surprised how quickly this deep material came out. I believe that the oral material is the main thing. The motto of her life, perhaps the motivation of suicide is: "I would rather be hated than disgusting." She becomes disgusted with herself, hates herself, then wishes to kill herself. It is interesting that both parents have some oral problems, too. The mother eats so much candy and gets so fat. The patient never wanted to identify with her mother who had rejected her. Her father drinks alcohol and is the one person to whom she turned, by whom she felt accepted. Rejection by him in the bathroom scene broke the one good relationship and the motif of disgust entered. She had to do a disgusting thing—had to wet the bed—after being spanked for wetting her pants. She was trying to test her parents to discover if she could be loved even though disgusting. She attempted to deny disgust by eating snow with dog feces to prove to herself that one should not be disgusted.

It seems that she gave up hope of being loved by mother or father. She tried to identify with father, tried to be a boy. Later she took to alcohol as he had done. When her feminine development became manifest it was disgusting to her. She attempted to deny the female role. The whole eating problem is associated with denial of femininity. It seems as if, to her, eating means becoming a pregnant woman. The stomach takes the place of the ovary. Food should not get in. While she craves it, she wants to vomit it. With her, eating seems to be confused with impregnation.

I would not dare say too much about the treatment. Relationship to Dr. Nemiah, being accepted by a male person, must mean a great deal to her. She really gives him a great deal of fantasy material. That will be the mainstay of therapy;—work through with her the fantasies, how eating means impregnation. Help her realize that fantasy is not reality. One might be able to convince her of her feminine role in life which she fears.

DR. LEMOYNE WHITE: I think that this patient, in common with patients who are infantile, tends to act out her feelings and be unconscious of them. She has had more difficulty in handling her hostile feelings toward Dr. Nemiah than has been apparent today in the presentation. She is having a difficult time making a relationship, and he will have to go through a lot of discouraging behavior on her part.

DR. FINESINGER: I think she differs from typical anorexia nervosa. Her episodes of starving fluctuate more rapidly. She reacts more rapidly to symbols than does a typical anorexia nervosa. Pills have some significance. She tries to handle the problem of rejection in ways that do not succeed. She is very ambivalent and that makes it difficult for her. I have the impression that Dr. Nemiah is doing well with her. She would not have told him all this unless he had a good start with her.

What are the best areas to approach? Would it be wise to go for suicidal situations? When she tries to kill herself, it seems that she is saying symbolically: "I have tried to identify with you, but you have rejected me. You'll be sorry when I'm dead." The function of the suicidal attempt is to stir up guilt in the other person, with the idea: "You'll be sorry when I've killed

myself." That is not unusual in children and immature people.

I believe that it would be profitable to focus the interviews back to her suicidal attempts. Ventilation of these experiences might lead into the problem of rejection. This case is more like hysteria than anorexia nervosa; her prognosis is better than that of a patient with typical anorexia. It would be worth while continuing psychotherapy with her.

DR. COBB: Have you seen her mother?

DR. NEMIAH: She is a short, fat, dumpy woman. She was very excitable after the patient had taken pills. She gets into temper tantrums, yells and screams. She has taken a horsewhip to the patient several times.

DR. COBB: That fits in with other histories in anorexia nervosa. The mother drives them one way or another. Some have had their first serious attack at eighteen or nineteen when the mother began to urge them to marry and had picked out a man.

This patient is not satisfied with the starvation; she has to try suicide but the suicidal attempts are not very realistic.

DR. FINESINGER: The patient probably knows that aspirin is not going to kill her. If this is so, the pills or the act of ingestion must have some symbolic meaning. The emphasis on symbolism and the "suicidal" attempts suggest hysteria as the most probable diagnosis.

DR. COBB: Many of these patients have been handed from hospital to hospital. They are labelled schizophrenia in one clinic and hysteria in the next. They go around the circle again. I have no doubt but they look like hysteria and schizophrenia. In the last seventeen cases we have had of undoubted anorexia nervosa there were four who succeeded in killing themselves. That is a fairly high rate of mortality. Six are married and over the anorexia nervosa and have families. The other seven make their hospital rounds still.

They all have remissions. A number have them over a year or two or three. Usually the sequence is a starvation episode then a remission of a few months or a year. They have four or five episodes and then either get over it or die. In this case the interesting aspect is that anorexia was not the main feature when she arrived, but the essence of the syndrome was learned through the interviews.

DR. FRANCES J. BONNER: I was impressed by the number of features of this case which are similar to those we have seen in many hysterias, particularly those which we have described as being very severe or very infantile. In that group one can find most of the features of this case, including oral pregnancy fantasies, ovaries in the stomach, etc.

DR. COBB: I may have exaggerated the specificity of this syndrome. Perhaps I ought to admit more of an intergradation with schizophrenia and hysteria. Anorexia nervosa was described as a syndrome by Gull in 1874 who wrote it up very well. As much as any syndrome in psychiatry I think it deserves a name.

DR. PAUL D. MACLEAN: How much significance do you give the depression?

DR. COBB: It is unusual. When these patients are starving and at their lowest some of them show a drive of energy. They are not manic in their stream of talk but show great motor activity. Others are depressed. This girl is the first one in whom I really considered manic-depressive psychosis.

Let us go ahead with her another month in the way we have. If we do not make headway, we will have to think of what next. How much psychoanalysis would help I do not know. She would be an interesting case for a control analysis.

FURTHER TREATMENT

Interviews were continued in the same manner. The patient was allowed to talk freely and spontaneously with a certain amount of "focussing" of the discussions around the suicidal attempts. These seemed to relate to a life-long pattern of behavior, i.e., when the patient developed strong positive feelings toward people (in her words, when she "got too close to people")

she would be impelled to break away. There would then be depression and the wish to die. No disturbing interpretations were made to her and the unconscious symbolism of the oral fantasies was not explained.

In the nine months since discharge the patient has not done well. Most of her symptoms have continued and she has made two more "suicidal" attempts. She has obtained and quit several jobs and joined Alcoholics Anonymous in an attempt to control her drinking. After a period of initial enthusiasm in which she immersed herself zealously in their activities, her interest waned. She quit A. A., discontinued psychotherapy and returned to live with her family. An indirect report from a member of her family indicates that her impulsiveness, mood swings and drinking are essentially as they were prior to treatment.

SUMMARY

This case of anorexia nervosa illustrates interesting psychodynamic mechanisms occurring in a girl whose symptoms also included alcoholism, tendencies toward drug addiction and rapid mood swings.

Typically, anorexia nervosa is characterized by periods of starvation, emaciation, amenorrhea and gastrointestinal discomfort. No primary metabolic or endocrine dysfunction has been established and in recent years there has been an increasing recognition of the importance of psychogenic factors. Some patients have disgust for food although literally starving. This has been found in some cases to be associated with fantasies of oral impregnation. The act of eating or the state of being fat therefore take on a profoundly disturbing symbolic significance.[1]

In many other cases no such fantasies are discovered. The patients may have no loss of appetite. They may stop eating in spite of great hunger, or they may eat and then vomit. The psychologic background may be expressed as merely a desire to remain slim and boyish. Sex may consciously enter the psychologic picture merely as an expression of the feeling that to be fat is to be voluptuous.[2]

In the staff discussion of this case the general characteristics of the syndrome were reviewed as well as interpretations of the patient's specific symptoms and life problems. In the treatment of such a patient hospitalization and persuasion to eat an adequate diet will often result in a remission, but this is not a cure. The illness is a serious one with a relatively high mortality rate; and unless the patient can be helped by means of psychotherapy to achieve a more adequate solution of her conflicts, the periods of starvation will probably continue, not infrequently accompanied by such serious neurotic symptoms as to necessitate committment to a mental hospital.

[1] WALLER, J. V., KAUFMAN, M. R. and DEUTSCH, F. Anorexia nervosa: a psychosomatic entity. *Psychosom. Med.*, 2: 3, 1940.

[2] DUBOIS, F. S. Compulsion neurosis with cachexia (anorexia nervosa). *Am. J. Psychiat.*, 106: 107, 1949.

Clinico-pathologic Conference

Weakness, Weight Loss and Prostration*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. S., (B.H. No. 31793), was a white, married woman, forty-three years of age, who entered the Barnes Hospital for the first time on October 17, 1931, complaining of swelling of the neck, nervousness, shortness of breath and loss of weight. The family and past histories were non-contributory. Twenty years before entry during her first pregnancy the patient noted enlargement of the right side of the neck which apparently did not increase in size. Fifteen years later during her second pregnancy she became nervous, irritable and emotionally unstable and continued to be so to a varying degree during the years which preceded her first admission. Six months prior to coming to the hospital she developed shortness of breath and palpitation on exertion, and at the same time noted that she felt warm and perspired easily. Although her appetite was excellent, she had lost 30 pounds in weight. When she consulted her physician fifteen days before entry, he noted a tremor, enlargement of the thyroid gland with a bruit and thrill but no lid lag. Her blood pressure was elevated. She was given Lugol's solution by mouth and was referred to the hospital for thyroidectomy.

Physical examination at the time of entry revealed a temperature of 37°C., pulse 100, respirations 20 and blood pressure 170/65. The patient appeared restless. Her hands were moist, the skin warm and her face flushed. There was evidence of weight loss. Neither exophthalmos nor lid lag was described but there was a tremor of the tongue, lips and fingers. Examination of the upper respiratory tract was negative. The thyroid gland was moderately enlarged, particularly on the right, but no thrill or bruit could be detected. The lungs were clear to percussion and auscultation. The heart was hyperactive. The maximal apical impulse was in the fifth interspace 10½ cm. from the midline. The rhythm was regular. A systolic murmur could be heard along the left sternal border. The peripheral pulses were bounding. The remainder of the physical examination was not remarkable.

The laboratory findings were as follows: Blood count: red cells, 4,260,000; white cells, 6,500; hemoglobin, 14.5 Gm.; differential count: within normal limits. Urinalysis: negative. Blood Kahn test: negative. Non-protein nitrogen: 27 mg. per cent; blood sugar, 117 mg. per cent; basal metabolic rate, +42. Electrocardiogram: low Q waves in Lead III.

Since the patient's condition had improved quite markedly during the fifteen days she took Lugol's solution before coming to the hospital, a subtotal thyroidectomy was performed shortly after hospital entry. The thyroid was twice normal size and both lobes were diffusely enlarged. No adenomas were present. Microscopic sections revealed changes characteristic of a diffuse toxic goiter. The patient's postoperative course was uneventful. She was discharged on November 7, 1931, and advised to continue iodine therapy.

For most of the sixteen years between her first and second admissions, the patient

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remained essentially well; ten months before her second entry she began to lose weight and at the end of six months had lost about 30 pounds. She was seen by her physician who told her that she had "mild hypertension," but the rest of the physical findings apparently were normal. A gastrointestinal series was said to have been negative; blood counts, an electrocardiogram, and the basal metabolic rate were also within normal limits. The patient, however, continued to lose weight; her appetite failed and she vomited occasionally. One week before admission weakness became so pronounced that she had to remain in bed most of the time. Her appetite then completely disappeared and she was able to take only small amounts of liquid. She slept most of the time and on the day prior to entry was almost totally unresponsive and incoherent, being unable to recognize her surroundings or acquaintances. During the week before entry she vomited three or four times. She was admitted to the hospital on May 10, 1947.

Physical examination at that time revealed a temperature of 36°c., pulse 94, respirations 14 and blood pressure 100/70. The patient was lethargic, incoherent and prostrated. When spoken to, she slowly turned her eyes in the direction of her questioner. The skin was inelastic and dry. There was marked evidence of weight loss. No abnormal pigmentation was seen. The pupils were equal and reacted to light and accommodation; the left pupil, however, was somewhat irregular. There was moderate nicking of the retinal vessels at the arteriovenous crossings and the left disc was not quite as well outlined as the right. No hemorrhages or exudates were seen. Examination of the upper respiratory tract was not remarkable. The tongue was dry and the mouth was edentulous. Examination of the neck was negative. The lungs were clear. The heart was not enlarged; the rhythm was regular and there were no murmurs but the sounds were rather muffled. The abdomen was soft but no organs or masses were felt. The legs were held rather rigidly and the fingers were flexed in a position which suggested mild carpospasm. The knee jerks, ankle jerks and abdominal reflexes could not be elicited. A suggestive Babinski sign was present on the right and a more definite one on the left.

The laboratory findings were as follows: Blood count: red cells, 4,500,000; hemoglobin, 12.8 Gm.; white cells, 3,000; differential count: eosinophiles, 2 per cent; stab forms, 5 per cent; segmented forms, 54 per cent; lymphocytes, 36 per cent; monocytes, 3 per cent. Urinalysis: albumin, 1+; sugar, negative; acetone, trace; sediment, negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 21 mg. per cent; blood sugar, 87 mg. per cent; CO_2 combining power, 15.3 mEq./L; chlorides, 73 mEq./L; total protein, 4.4 Gm. per cent; albumin, 2.9 Gm. per cent; globulin, 1.5 Gm. per cent. X-ray films of the skull were indeterminate. An electrocardiogram showed a P-R interval of .24 seconds.

The patient was given fluids parenterally and took some water by mouth. Early in the morning of the second day she complained of discomfort in the suprapubic region and on catheterization, 1,200 cc. of urine were withdrawn. At that time her blood pressure had fallen to 60/45. The patient was given an infusion of plasma to which adrenocortical extract was added. She also received 2,000 cc. of 5 per cent glucose in saline parenterally and 20 mg. of desoxycorticosterone acetate intramuscularly. Two-tenths of 1 cc. of epinephrine were given subcutaneously and following the plasma and fluids she received 25 cc. of adrenocortical extract intraveously. Oxygen therapy by nasal catheter was begun. The patient's blood pressure rose to 100/60 and her lungs remained clear. She became incontinent of urine and stools and her temperature rose to 38°c. Several hours later she vomited dark material; she continued to be extremely listless. Following additional amounts of adrenocortical extract intravenously, the patient's blood pressure rose

to 110/65. On the afternoon of the second day, however, it fell to 58/45 and the radial pulses became barely palpable. The patient was stuporous and her respirations were deep and stertorous. A lumbar puncture was performed and the spinal fluid was found to be entirely normal. A repeat white blood count showed 12,800 cells with 22 stab forms and 42 segmented forms. By 5 P.M. of the second day she was comatose. No clinical evidence of dehydration was present and re-examination revealed no pigmentation of the mucous membranes. She continued to receive intensive supportive therapy including plasma infusions, glucose, saline and adrenocortical extract. Despite these measures, however, early in the morning of May 12, 1947, she expired. Just before death her temperature was noted to be 38.8°C.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: In this very interesting case the history is rather straightforward. The patient, who had apparently been well most of her life, at the age of 43 developed rather classical thyrotoxicosis and following thyroidectomy was well for the ensuing 15 years. The illness which led to her death was of approximately ten months' duration, the patient's final episode being characterized by prostration. Dr. Wade, would you care to open the discussion?

DR. LEO J. WADE: I should like to ask several questions which were not answered in the protocol. First of all, was this patient's menstrual history normal? Second, what do we know of her emotional stability? And third, were there any changes in hair distribution?

DR. ALEXANDER: As far as is known, the patient's menstrual history was not remarkable. She was, however, known to be a very emotional individual. Her hair distribution was apparently normal. Why do you ask these questions, Dr. Wade?

DR. WADE: This patient apparently had multiple endocrine abnormalities and my questions were directed toward determining whether additional evidence of endocrine inbalance was present. For example, it occurred to me that this patient may have had anorexia nervosa. In some respects the history suggests panhypopituitarism but the absence of menstrual difficulties and abnormalities of hair distribution are against that diagnosis. One must certainly consider Addison's disease which may give rise to a clinical picture such as was seen here. The relationship between the thyroid and the adrenal gland is indeed a complex one, and the effect of dysfunction in one may be reflected by changes in the other. I believe that this patient did not have Addison's disease; I would favor anorexia nervosa.

DR. WILLIAM H. OLMSTED: There are a number of factors in the history which are strongly against the diagnosis of Addison's disease. I do not remember a case of terminal adrenal insufficiency in which both the non-protein nitrogen and the blood sugar were normal. Further it is said that during the course of her last illness she was found to have hypertension and a normal basal metabolic rate. Both of these findings are uncommon in Addison's disease.

DR. ALEXANDER: I was informed that when this patient was seen about six months before entry, her systolic blood pressure was 180, and one month before entry and thus approximately one month before death it was said to be 130.

DR. OLMSTED: If the patient indeed had a blood pressure of 180 and, as was described in the protocol, she had evidence of retinal sclerosis, I would bring up the possibility of a cerebral vascular accident having been responsible for her terminal picture.

DR. ALEXANDER: Dr. Olmsted, would you tell us what signs and symptoms you think are essential to the diagnosis of Addison's disease? Are there any which you consider *sine qua non* for that diagnosis? Does the presence of hypertension enable one completely to exclude adrenal insufficiency?

DR. OLMSTED: It should be pointed out that when this patient entered the hospital she was semistuporous, and it is very difficult often in that situation to obtain certain relevant information. Low serum chlorides,

of course, suggest adrenal insufficiency and in this patient that finding was present. Excessive amounts of chloride in the urine substantiate the possibility. In a patient whose condition is not terminal I expect the systolic blood pressure usually to be below 110 mm. of mercury. A history of fatigue is helpful. The presence of increased pigmentation is important although Addison's disease may not always be accompanied by hyperpigmentation. Like so many other syndromes adrenal insufficiency may be extremely variable in its signs and symptoms although those I have mentioned are most commonly seen.

DR. ALEXANDER: Do you believe that weight loss is important to the diagnosis?

DR. OLMSTED: Yes. In the absence of weight loss I would doubt seriously the diagnosis of Addison's disease.

DR. ALEXANDER: Dr. MacBryde, what criteria do you consider necessary for the diagnosis of adrenal insufficiency?

DR. CYRIL M. MACBRYDE: Increasing fatigue and asthenia are the symptoms which are most suggestive of Addison's disease. In some few patients all the other symptoms and signs may be absent. The blood pressure may be within so-called normal limits and there may be no pigmentation or weight loss. Indeed, the patient may be overweight. Of course, most patients do exhibit the features which Dr. Olmsted has outlined, but I think it is important to point out that Addison's disease may occur without hypotension, without weight loss, without gastrointestinal disturbances and without pigmentation. By the time adrenocortical insufficiency has progressed to the crisis, however, one expects at least hypotension and weight loss.

DR. ALEXANDER: Then in view of the fact that one of the features of this patient's final illness was progressive asthenia, you would certainly entertain the diagnosis of adrenal insufficiency?

DR. MACBRYDE: Yes. I think it has to be given serious consideration in view of the history. I do not think that we have sufficient data to be sure since many other diseases may be accompanied by weakness and weight loss. For example, extensive carcinoma may give rise to a clinical picture very similar to the one that is seen here. A cerebrovascular accident, as suggested by Dr. Olmsted, might likewise be responsible. A diffuse panendocrine disorder such as Simmonds' disease must be considered, and as Dr. Wade pointed out anorexia nervosa cannot be ruled out.

DR. ALEXANDER: I believe it is of importance to remember that this patient was ill over a period of ten months with progressive weight loss, progressive asthenia and eventually prostration. When she came in, her serum chlorides were certainly very low.

DR. MACBRYDE: Although hypochloremia is characteristic of Addison's disease in crisis, this patient had vomited a good deal and prolonged vomiting may also cause reduction in the serum chloride.

DR. HAROLD BULGER: This patient was presumably dehydrated on entry. In view of that fact, the low carbon dioxide combining power and chlorides are suggestive of decreased serum sodium, a finding which would be in keeping with adrenocortical insufficiency.

DR. MACBRYDE: It would have been of great help to have determined the blood sodium and potassium. The patient was in the hospital only a short time however, and these determinations were not made. In regard to the question of pigmentation in Addison's disease, Soffer in his book states that of his forty-six patients with the disease only one was free of abnormal pigmentation;[1] Thorn noted a characteristic pigmentation in 94 per cent of the 158 patients he followed.[2] On the basis of such figures the diagnosis of Addison's disease in a patient who exhibits no abnormal pigmentation can be questioned.

DR. ALEXANDER: It should be pointed out that all the patients who are classified as having increased pigmentation may not

[1] SOFFER, L. J. Diseases of the Adrenals. 2nd ed. Philadelphia, 1948. Lea and Febiger.

[2] THORN, G. W., DORRANCE, S. S. and DAY, E. Addison's disease; evaluation of synthetic DOCA therapy in 158 patients. *Ann. Int. Med.*, 16: 1,053, 1942.

exhibit diffuse pigmentation or increased amounts in the body creases or the mucous membranes. Some of them exhibit black freckles or moles only.

DR. MACBRYDE: I agree with you. Some patients with proved Addison's disease have only slight increase in pigmentation which may, as you point out, take the form of the occasional black freckles. If such patients are followed, as their disease progresses pigmentation may increase markedly. We have had one case of proven Addison's disease in a redheaded man who had no abnormal pigmentation whatsoever.

DR. ALEXANDER: If we assume that this patient did have Addison's disease, I should like to ask Dr. Wade if he would tell us the current thought in regard to the etiology of this syndrome. How often is tuberculosis the cause of Addison's disease?

DR. WADE: Opinion on that question varies from one series of patients to another. In general it is thought to be responsible for a large number of cases; in some series figures up to 90 per cent are given. Perhaps Dr. Robert Moore could tell us what the pathologists' current view on this point is.

DR. ROBERT A. MOORE: In one series of 566 cases collected from the literature the incidence of tuberculosis of the adrenals was about 70 per cent.[3]

DR. ALEXANDER: In Dr. Thorn's large series the majority were non-tuberculous. On the other hand if one considers the collective series which Dr. Moore has just reported, one might raise the question as to whether patients with Addison's disease should be given streptomycin empirically. We are very fortunate in having Dr. Walsh McDermott of the Department of Medicine of the Cornell Medical School here today. He has had a substantial experience in the treatment of tuberculosis with streptomycin and I would like to ask him to comment on this point.

DR. WALSH MCDERMOTT: We have recently seen one patient with Addison's disease who developed a cold abscess of the psoas muscle without apparent involvement of bone. The adrenal insufficiency was controlled by the usual measures; although we did not think that we would either influence its course or that of the psoas abscess, we treated the patient with streptomycin. We employed the same regimen which we would use in the treatment of tuberculous empyema, that is, both systemic and local streptomycin. For several months the antibiotic exhibited a favorable effect on the abscess but subsequently the lesion flared up and showed no response to further streptomycin therapy. No change in the course of the Addison's disease was seen. One could have predicted that no change would be noted; since by the time the clinical syndrome of adrenal insufficiency had appeared, it is quite likely that so much adrenocortical tissue has been destroyed that even if the tuberculous lesions would respond completely little clinical improvement in the adrenal insufficiency would be obtained. It is conceivable that the course of very early Addison's disease due to tuberculosis might be favorably influenced if an agent is developed which is as effective against the tubercle bacillus as penicillin is, for example, against the hemolytic streptococcus.

DR. ALEXANDER: Dr. Futcher, adrenocortical insufficiency may appear in endocrine disorders other than Addison's disease. Are there any differences in the chemical findings in adrenocortical insufficiency *per se* or in that seen in Simmonds' disease?

DR. PALMER H. FUTCHER: I Think that crisis is much more common in Addison's disease than it would be in Simmonds' disease with mild adrenal insufficiency. I believe that this patient's course was typical of classical Addison's disease.

DR. ALEXANDER: Isn't the finding of a normal N.P.N. unusual in a patient only two days from death due to adrenal insufficiency?

DR. FUTCHER: I agree that it is most unusual; commonly it is elevated, reflecting changes in the kidneys secondary to de-

[3] GUTTMAN, P. H. Addison's disease. A statistical analysis of 566 cases and a study of the pathology. *Arch. Path.*, 10: 742, 895, 1930.

creased plasma volume and possibly changes in the arteriolar vessels themselves.

DR. ALEXANDER: Is a normal blood sugar atypical?

DR. FUTCHER: That finding does not surprise me nearly as much as a normal nonprotein nitrogen. Adrenal crisis may be characterized chiefly by deficiency of cortical hormones other than those which govern carbohydrate metabolism.

DR. ALEXANDER: Don't you think that in a fatal Addisonian crisis the blood sugar is likely to be low?

DR. FUTCHER: I have no definite information on that point but perhaps Dr. MacBryde has.

DR. MACBRYDE: The blood sugar during the crisis of adrenocortical insufficiency may be within normal limits not infrequently. In my experience more patients in crisis have normal blood sugars than low blood sugars although, of course, hypoglycemia is not uncommon.

DR. ALEXANDER: Is that your experience, Dr. Olmsted?

DR. OLMSTED: Offhand, I cannot recall a sufficient number of cases to be sure.

DR. ALEXANDER: What about the low CO_2, Dr. Futcher?

DR. FUTCHER: A low CO_2 is rather uncommon in Addisonian crisis and the exact reason for its occurrence is not known. It is possible that the kidney loses more sodium than chloride in some instances; if such were the case, the CO_2 might be reduced.

DR. ALEXANDER: I am sure that if the patient had been in the hospital longer, the blood sodium would have been determined.

DR. FUTCHER: We could have determined the serum sodium during the crisis, but it would almost certainly have been depressed since both the chloride and carbon dioxide were very low. The potassium probably would have been elevated. Other than those two determinations, which probably would not have been of particular aid in her treatment, no other studies were indicated during the crisis.

DR. ALEXANDER: Could you comment on the procedures which are used in confirming a tentative diagnosis of Addison's disease?

DR. FUTCHER: Probably the most valid test is the Cutler-Wilder salt restriction test which involves the withdrawal of salt from the diet for several days and the observation of urine chloride excretion which in the Addisonian is above normal. An alternate procedure which is less dangerous is the Kepler-Power water test. Here the patient is observed to see if a rapid diuresis occurs after the ingestion of a large amount of water. In a patient with adrenal insufficiency such a rapid diuresis is not possible. The Kepler-Power water test is not as specific in confirming the diagnosis of Addison's disease as is the Cutler-Wilder test. On the other hand, it is much safer.*

DR. ALEXANDER: Is the glucose tolerance curve of any value?

DR. FUTCHER: In patients with Addison's disease the glucose tolerance curve is flat, presumably due to difficulty in the absorption of glucose. Intravenous glucose tolerance tests show an essentially normal peak and a tendency to relatively marked hypoglycemia several hours later.

DR. ALEXANDER: Dr. Schroeder, would you comment on the changes in the blood pressure and their cause?

DR. HENRY A. SCHROEDER: At least four factors are operable, namely, the blood volume, blood viscosity, cardiac output and the state of the arterioles. Disturbance in any one of these may lead to hypotension. This patient probably had a considerably reduced blood volume. Occasionally, patients with hypertension exhibit lower blood pressures when their blood volume is low. This patient's cardiac output was probably reduced, perhaps partly due to low blood volume and partly due to an endocrine induced electrolyte disturbance. She may

* This case was discussed in October, 1947, prior to the publication of the studies of Thorn and his associates[4] recording another approach to this problem (footnote).

[4] THORN, G. W., FORSHAM, P. H., PRUNTY, T. G. and HILLS, A. G. The response to pituitary adrenocorticotrophic hormone as a test for adrenal cortical insufficiency. *J. A. M. A.*, 137: 1,005, 1948.

have had some nephrosclerosis because there is a history of hypertension and slight eye-ground changes. Experimentally, the adrenals and many other organs as well are necessary for the maintenance of hypertension; clinically they must likewise exhibit normal function for maintenance of high or normal blood pressures.

DR. ALEXANDER: Do I infer from your last remark that you think that the adrenal medulla may be of importance in this aspect of the disease?

DR. SCHROEDER: No, I believe that the hypotension of Addison's disease reflects cortical destruction although even hypertensives, who become extremely ill and debilitated, may have normal or even low pressure without adrenal cortical atrophy.

DR. ALEXANDER: What is the explanation for the postural hypotension often seen in Addison's disease?

DR. SCHROEDER: It may be due either to reduced blood volume or to the relaxed state of the arterioles. When these patient's are treated with DCA, the blood pressure rises and may reach true hypertensive levels. Dr. Perera in New York studied a number of patients with Addison's disease and found that with DCA and salt the blood pressure could be raised to rather high levels in about half of them.[5] We have had a similar experience here.

DR. ALEXANDER: Dr. Massie, what do you think the heart will show in this case?

DR. EDWARD MASSIE: In patients with Addison's disease the heart is characteristically small; but if this patient really had had hypertension previously and some vascular disease, her heart may be normal in size or even slightly enlarged.

DR. ALEXANDER: Dr. Wood, do you have any comments to make?

DR. W. BARRY WOOD, JR.: Dr. MacBryde showed several years ago that there is danger attached to giving patients with Addison's disease largea mounts of DCA without potassium, for under such circumstances the blood potassium may be lowered to a point where definite cardiac damage occurs. It has been shown experimentally that animals given potassium-deficient diets develop cardiac lesions. In this particular case the fact that the patient failed to respond to rather adequate treatment makes me wonder whether she did not have a very active tuberculous lesion. It seems to me that in most patients whose Addison's disease is in its first crisis, treatment of this order would produce a favorable response.

DR. ALEXANDER: Your point is well taken. Dr. Futcher, I believe you saw this patient. Would you comment on her therapy?

DR. FUTCHER: In retrospect, it is conceivable that this patient should have received even larger doses of adrenocortical extract and of fluids than she was given. However, as Dr. Robert Loeb has pointed out, there are patients with Addison's disease who may, when in crisis, not exhibit severe electrolyte and carbohydrate inbalances but who, despite adequate therapy, die in shock. There are certainly many factors which govern the response, in a given case, to treatment of Addisonian crisis.

DR. ALEXANDER: Are there any questions?

STUDENT: Was the prolonged P-R interval peculiar to Addison's disease or does it represent a potassium effect?

DR. MASSIE: The finding of delayed auriculoventricular conduction as evidenced by a P-R interval of 0.24 seconds is not uncommon in a patient who is in shock.

STUDENT: Can one postulate the reactivation of latent tuberculosis on the basis of the iodine therapy following thyroidectomy?

DR. MCDERMOTT: There is insufficient evidence at the present time to answer that question. In this patient, however, the iodine had been given some fifteen years before her terminal episode and it seems most unlikely that it was of importance.

STUDENT: Was there any explanation of the neurologic findings which this patient exhibited?

DR. ALEXANDER: That is a very good question. Dr. MacBryde, are there specific neurologic lesions in Addison's disease?

[5] PERERA, G. H., KNOWLTON, A. I., LOWELL, A. and LOEB, R. F. Effect of DOCA on the blood pressure of man. *J. A. M. A.*, 125· 1,030, 1944.

DR. MACBRYDE: I do not think they are part of the syndrome, Dr. Alexander.

STUDENT: Should chronic glomerulonephritis be included in the differential diagnosis?

DR. FUTCHER: Although it is true that so-called salt-losing nephritis may produce a picture resembling that of adrenocortical insufficiency, I believe the low normal N.P.N. in this instance would be against that diagnosis.

DR. ALEXANDER: In summary, I believe we all believe that this patient had adrenal insufficiency and died in a crisis which failed to respond to therapy.

Clinical Diagnosis. Adrenal insufficiency (Addison's disease); in crisis.

PATHOLOGIC DISCUSSION

DR. HENRY LANG: The skin of the lower chest showed fine brownish pigmentation. The heart was small, weighing 230 Gm. There was distinct dilatation of the left atrium and moderate fibrous thickening and stenosis of the mitral valve. The coronary arteries were markedly thickened, tortuous and partially occluded by calcified plaques. There were irregular grey foci of fibrous tissue in the muscle of the left ventricle, left auricle and anterior septum. The lungs were small and the middle lobe of the right lung was hypoplastic. The parenchyma was moist and of increased consistency with scattered rubbery foci of atelectasis. No active lesions of tuberculosis were present, but there were calcified and fibrous nodules in all lobes of the lungs and in the right tracheobronchial lymph nodes there were similar nodules measuring 2 to 3 mm. in diameter.

The adrenal glands were of normal size. On section there were nodules 2 to 10 mm. in diameter, of greyish-white, firm tissue surrounded by a zone of brownish pigmentation which replaced all but a narrow zone of recognizable cortex. In the other organs there were no significant changes except for congestion of the liver and spleen. When the spinal cord was cut, the substance bulged markedly; there was an advanced congestion of all of the central nervous system but no recognizable lesions.

DR. R. A. MOORE: The anatomic findings in this case are those of tuberculosis of the adrenal glands without active tuberculosis elsewhere in the body. The only other indications of such an infection were the calcified nodules in the lung, lymph nodes, liver and spleen, which were of the type and distribution generally interpreted as the healed lesions of first-infection tuberculosis. By and large, tuberculosis of the adrenal glands is a complication of reinfection tuberculosis. This patient apparently was not suffering from reinfection tuberculosis of the usual type, and one must assume that the lesions were in some way related to the first infection.

The first illustration (Fig. 1) is from a section of the adrenal gland; on the left a small amount of adrenal substance remains. Next to the few adrenal cortical cells there is a thick layer of fibrous tissue and then a zone of necrosis with heavy cellular infiltration. In Figure 2 this type of lesion is better illustrated. The small granulomas are sharply circumscribed and surrounded by fibrous tissue which is infiltrated largely with mononuclear cells and a few polymorphonuclear leukocytes. The granulomatous lesions are in part made up of living cells and in part of necrotic cells with sharp demarcation between the necrotizing lesions and the surrounding tissue. In Figure 3 the edge of a larger lesion with giant cells embedded in the surrounding fibrous tissue is illustrated. The microscopic appearance of these lesions is that of tuberculosis; acid-fast bacilli were identified within them. Thus the diagnosis of tuberculosis of the adrenal gland was established.

The next illustration (Fig. 4) is from a section of the thyroid gland. We were interested in the thyroid for two reasons: First, the patient had a subtotal thyroidectomy sixteen years before death but at the time of autopsy the thyroid gland was of normal size and composed of two lobes; second, at times there are changes in the thyroid in Addison's disease, particularly in the types caused by cytotoxic atrophy of the adrenal gland. The changes in the thyroid in such cases resemble those of

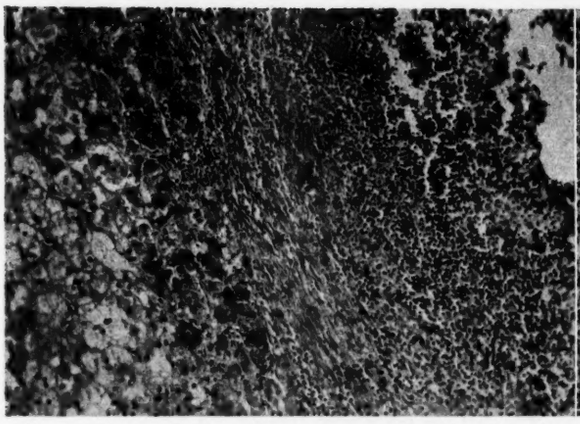

FIG. 1. Edge of tuberculous lesion of the adrenal with an adjacent small number of persistent cortical cells.

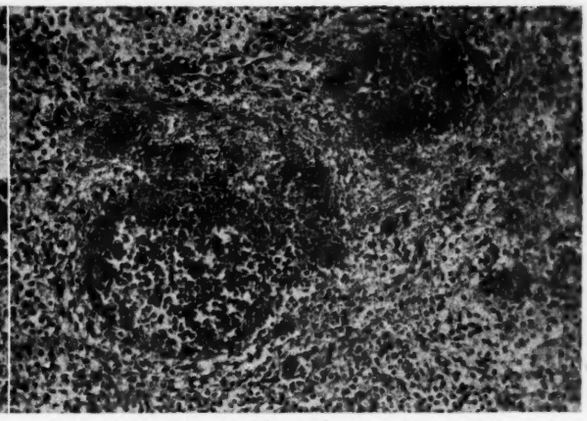

FIG. 2. Partially necrotic granulomas of tuberculosis in the adrenal gland. The stroma of the gland is extensively destroyed and replaced by fibrous tissue.

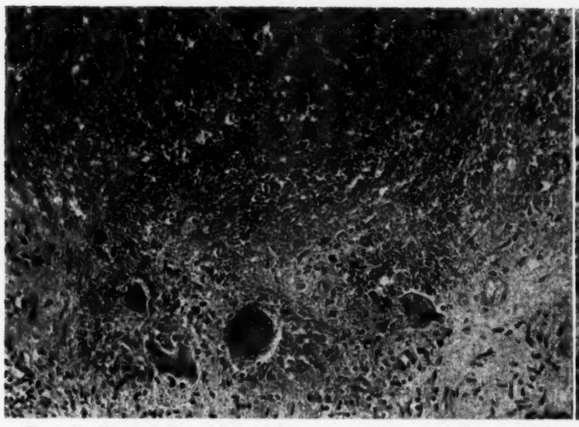

FIG. 3. Edge of a tuberculous granuloma with typical necrosis, fibrosis and giant cells. Acid-fast bacilli were identified in similar sections.

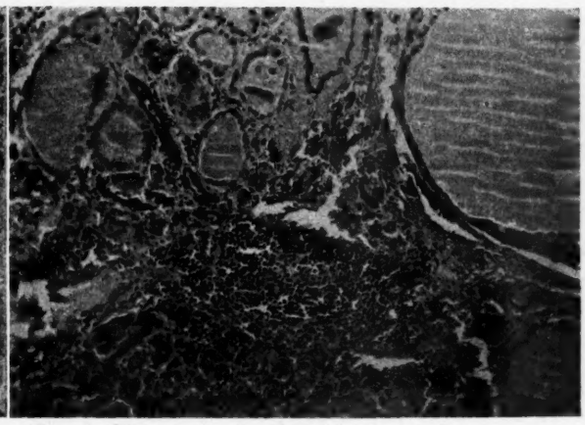

FIG. 4. Changes in the thyroid present sixteen years after subtotal thyroidectomy. The infiltration of lymphocytes and moderate storage of colloid are the most prominent features.

Hashimoto's disease in that there is a great increase of lymphoid tissue between the lobules of the thyroid. There is a moderate increase of such tissue in this section but the acini of the thyroid vary greatly in size. There is moderate storage of colloid. As lymphocytic infiltration and the formation of lymphoid tissue also occur in the thyroid gland in hyperplasia associated with hyperthyroidism, I am unable to decide whether the anatomic changes in this instance represent the residuum from old hyperthyroidism or whether they are part of Addison's disease. Certainly they are quite consistent with the changes that I have seen in Addison's disease.

In Figure 5 a section of the myocardium is seen which shows the focal fibrosis present in the sites described grossly. This change in the heart was probably the result of coronary insufficiency inasmuch as there was a moderate to advanced degree of coronary arteriosclerosis. The other possibility is, of course, that this change might have resulted from the episode of hyperthyroidism, inasmuch as the administration of thyroid substance to animals will lead to foci of necrosis in the heart muscle. That possibility seems to me unlikely since the hyperthyroidism had occurred so many years before the patient died of Addison's disease.

The last illustration (Fig. 6) is from the liver. It is incidental to the case but demonstrated very well the appearance of the liver after a patient has received large amounts of glucose. There is a large amount of glycogen in the liver cells which gives the cytoplasm a reticulated, almost vacuolated appearance. In many places the nuclei

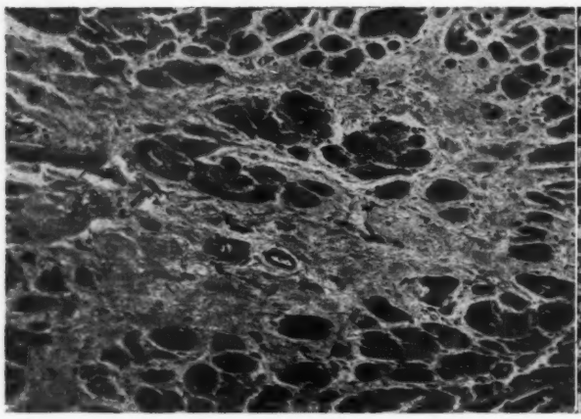

FIG. 5. Focal interstitial fibrosis of the myocardium of the type usually associated with coronary arteriosclerosis.

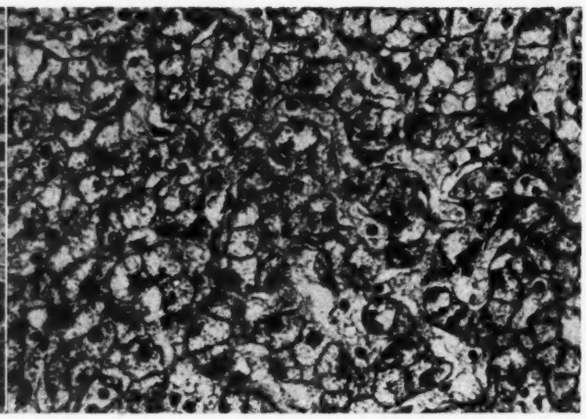

FIG. 6. Vacuolated hepatic cells with rarefied cytoplasm and "floating nuclei." The changes reflect both the low plasma proteins and the large amounts of glucose received shortly before death.

are the so-called "floating nuclei." This section of liver probably also reflects a relative depletion of proteins as the plasma proteins were about 4.4 Gm. per cent.

It should be remembered that Addison's disease, so far as I am aware, is not a diagnosis based on pathologic anatomy. Addison's disease is basically a physiologic disturbance. Pathologic anatomists may find tuberculosis of the adrenal gland quite comparable to what was present in this patient and with what appears to be total or partial destruction of the adrenal cortex and of the adrenal medulla, and yet the clinical history may give no clue that the patient had any of the physiologic disturbances that make up this syndrome. This patient had anatomic changes compatible with Addison's disease, and that observation is supported by the clinical findings previously discussed.

Tuberculosis of the adrenal glands is the most frequent lesion responsible for Addison's disease. In Guttman's review of 566 cases, 70 per cent had tuberculosis of the adrenals, 16 per cent had primary cytotoxic degeneration, and there were other causes of varied type including less than 1 per cent due to other infections and 1.7 per cent due to amyloid disease of the adrenal. In about 1 per cent of the cases no demonstrable lesion was recognized in the adrenals. It is also of interest that in analysis of the degree of pigmentation in 209 of the cases, Guttman demonstrated it to be directly proportional to the duration of the disease.

In regard to a few other aspects of this case, such as the condition of the heart and the cardiovascular system, this patient did have arteriosclerosis and fibrosis of the myocardium. We were not impressed, however, with the part that cardiac failure might have played in the terminal illness. There was no fluid in any of the cavities; and although there was congestion of the organs, the congestion was acute rather than chronic. Consequently, we have listed arteriosclerosis and myocardial fibrosis as accessory diagnoses. The pituitary gland was essentially normal; I do not believe that it played any part in this patient's illness. The only anatomic findings related to the signs in the central nervous system were congestion of the central nervous system which was quite marked and evidences of edema of the spinal cord.

Final Anatomic Diagnoses. Tuberculosis of the adrenal glands (clinical diagnosis of Addison's disease); bronze pigmentation of the skin of the anterior chest; fibrous nodules with calcification and anthracosis in all lobes of the lungs; calcified nodules in the right tracheobronchial lymph nodes and in the spleen.

Acknowledgment: The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

Case Reports

Coarctation of the Aorta*

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At this time when such remarkable strides are being made in vascular and cardiac surgery, it seems desirable to report a case of coarctation of the aorta which was found in a man aged seventy-two years. This case is particularly interesting because of the characteristic x-ray findings which are discussed in some detail.

No attempt is made to review the extensive literature on this subject; however, it is worth noting that in 200 cases collected from the literature by Abbott[1] in 1928 only two patients were over seventy years of age.

CASE REPORT

O. S., a seventy-two year old white man was admitted to the University Hospital on April 5, 1948, complaining of shortness of breath and swelling of his feet and ankles. The present illness began two years prior to admission with a severe coughing spell which came on suddenly, lasted for several hours but produced no blood or sputum. The patient had been working daily until the time of onset; there was no unusual physical exertion associated with the coughing spell. His physician was consulted and he advised bed rest for six weeks. The patient was asymptomatic at rest but when he resumed activity he noted dyspnea. There had been a gradual aggravation of dyspnea with development of orthopnea during the past two years. For the past eight months he had not been able to walk more than a block at a time and had had ankle edema.

He had been on a restricted salt intake, i.e., reduction in the amount of salt used in preparing food, but had eaten ordinary bread and butter. He had received ½ tablet of digitalis daily for the past two years and during the eight months prior to admission had received a mercurial diuretic about once a week.

At the age of twenty-two he had been refused life insurance because of an "enlarged heart" and hypertension. He had had the usual childhood diseases and had had a subtotal gastric resection in 1943 because of a benign pyloric ulcer. At the time of surgery notching of the ribs and cardiac enlargement had been noted on x-ray examination and the diagnosis of coarctation of the aorta was suggested. He had recovered satisfactorily from his surgery and had been able to eat a relatively adequate diet. The family history and review by systems were non-contributory except as noted above.

Physical examination revealed the temperature to be 98.8°F., pulse 85, respirations 20. The pupils were equal and reacted to light and accommodation. The optic fundi showed only very minimal arteriolar sclerosis without spasm. The remainder of the examination of head and neck showed nothing abnormal. Large, tortuous, pulsating blood vessels were noted about both scapulae. The lungs revealed moist rales at both bases. Blood pressure was 180/110 in arms and 130/85 in legs. The left border of the heart was at the anterior axillary line in the fifth and sixth interspaces. No thrills were noted. There was a presystolic gallop rhythm at the apex with a soft systolic murmur. A well healed upper abdominal surgical scar was noted. Liver, spleen and kidneys were not palpable. No other abnormalities were noted. The prostate was slightly enlarged, smooth and non-tender. There was pitting edema of ankles and legs. Femoral pulsations were noted but popliteal and dorsalis pedis pulsations were absent.

Urinalysis revealed a specific gravity of 1.024; normal chemically and microscopically. Hemoglobin was 13.9 Gm.; white blood cells 10,200 with 63 per cent neutrophiles; blood urea nitrogen 20 mg. per 100 cc.; serum albumin 4.0 Gm. and serum globulin 2.2 Gm. per 100 cc.; the Kline test was negative; venous pressure was 12.7 cm. of citrate in arms; vital capacity 2.8 L. (63 per cent of expected normal). An electro-

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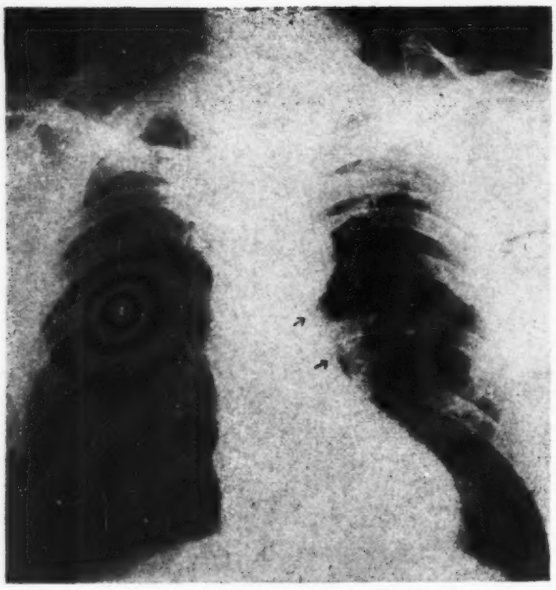

FIG. 1. Frontal view of chest July 19, 1943. Upper arrow: dilated proximal portion of left subclavian artery. Lower arrows: left border of descending aorta. Note left ventricular enlargement of heart and marked notching of inferior surfaces of ribs.

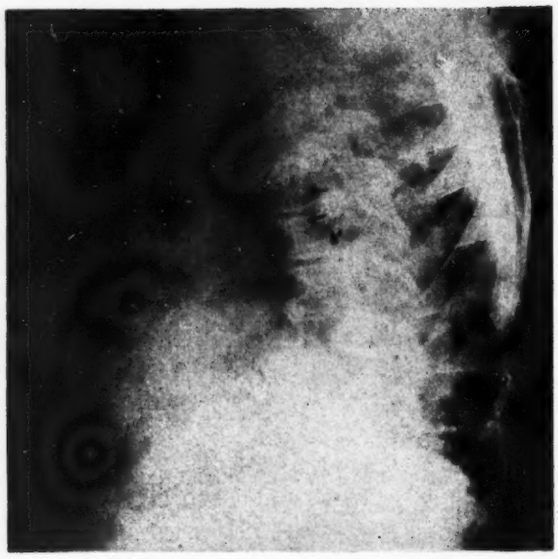

FIG. 2. Left anterior oblique view of chest April 6, 1948. Arrows point to notched shadow possibly representing narrowing at isthmus of aorta with dilated subclavian artery above. Note poor visualization of transverse portion of the aortic arch.

cardiogram showed frequent ventricular extrasystoles and a left bundle branch block, a finding which had been present in 1943.

An x-ray (Fig. 1) taken on July 19, 1943, showed moderate cardiac enlargement with prominence of the left lower pole of the silhouette indicating left ventricular enlargement. The convexity of the ascending aorta was just visible along the right mediastinal contour but the prominence was insufficient to indicate significant enlargement of the ascending aorta. Along the left upper mediastinal contour there was a rounded projecting soft tissue shadow at the level where the aortic knob is normally found. The pulmonary artery shadows appeared normal. The waist-line of the heart along the left border was rather deep, and just within the cardiac contour at the level of the waist-line a second contour was visible suggesting descending aorta. This contour at its upper margin made a rather deep notch with the shadow of the projection which was presumed to represent aortic knob. Very extensive notching of the inferior aspects of the posterior portions of the lower ten ribs bilaterally could be visualized.

Fluoroscopic examination and chest films of April 6, 1948, showed marked increase in the size of the heart, again predominantly involving the left ventricle. There was at this time elevation of the soft tissue zone at the left base with evidence of pleural effusion laterally, and a left lateral decubitus film demonstrated that the increased soft tissue zone at the left base represented partially loculated pleural fluid over the surface of the diaphragm. There was also a small right pleural effusion. The findings with respect to the rib notching and the upper cardiac and mediastinal contours on the left side were unchanged, the appearance still suggesting the presence of a rather prominent aortic knob. Examination in the left anterior oblique view (Fig. 2) revealed a lack of visibility of the transverse portion of the aortic arch. In this same left anterior oblique view there was a suggestion of a notched soft tissue shadow superimposed on the outline of the spine at a level corresponding rather closely with that expected for the isthmus of the aorta. This last finding was not definite and perhaps without significance although the position of the shadow suggested that it might represent the narrowed isthmus with the dilated subclavian above.

The patient was placed upon a diet which contained less than 1 Gm. of salt per day and the digitalis was increased until the patient exhibited the early symptoms of digitalis toxicity. In the course of a week the patient lost 9 pounds in weight (from 154 to 145), the rales in his lungs disappeared and dyspnea was no longer evident. The vital capacity rose to 3.41 L. (80 per cent) and venous pressure fell to 6.2 cm. of citrate.

He was completely ambulatory at the time of discharge from the hospital. He was instructed to continue on the low salt diet and to take 0.2 mg. of digitoxin daily.

COMMENT

This case seems worthy of report because of several interesting findings. In a man who had had significantly elevated blood pressure for fifty years, the changes in the vessels of the optic fundi were minimal or even "within normal limits for the patient's age," as reported by the ophthalmologist. This would seem to lend support to the theory that the vascular changes in the optic fundi as seen in essential hypertension are the product of more than the elevated blood pressure.

The fact that this patient attained an age of seventy years before he was embarrassed by a failing heart might lend support to the theory that these patients get along well until some other factor is added which leads to heart failure. In this particular case one might as well attribute the heart failure to arteriosclerotic heart disease as to coarctation. One might also theorize as to varying degrees of coarctation and believe that this represented a low degree of aortic obstruction. However, the degree of collateral circulation established would argue against such a hypothesis.

Two of the common clinical findings in coarctation of the aorta were not demonstrable in this patient, namely, the basal systolic murmur and absent femoral pulsations, yet the findings dependent upon collateral circulation were very apparent. It is possible that the low position of the aortic arch might explain the absence of the typical basal systolic murmur.

The rib notching in this case was quite extensive and pronounced and was entirely characteristic of coarctation of the aorta. The shadow suggesting a prominent aortic knob in the presence of definite clinical and roentgen evidence of coarctation is of interest since one of the usually helpful roentgen signs is the inconspicuousness of the aortic knob. In the present case visualization of the shadow of the left border of the descending aorta well within the heart border was taken as evidence that the upper vascular projection was actually the dilated proximal portion of the left subclavian artery. Gladnikoff[2] has recently called attention to this finding in cases of coarctation of the aorta and also has attributed the poor visibility of the transverse portion of the aortic arch in the left oblique view to shortening and downward or medial retraction of the aortic arch.

SUMMARY

A report is made of a case of coarctation of the aorta diagnosed in a man aged seventy-two years by clinical vascular findings and x-ray evidence. This patient has lived an active life despite signs of right and left ventricular failure. He responded well to ordinary treatment for congestive failure.

REFERENCES

1. Abbott, Maude E. Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. *Am. Heart J.*, 3: 392 and 574, 1928.
2. Gladnikoff, H. The roentgenological picture of the coarctation of aorta and its anatomical basis. *Acta radiol.*, 27: 8, 1946.

Regional Enteritis Complicated by Pylephlebitis and Multiple Liver Abscesses*

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THE usual and expected complications of regional enteritis are varying degrees of intestinal obstruction, local abscesses, perforation, fistulas and frequent bowel dysfunction with its attendant inanition and anemia. Recently a patient with this disease was studied at the University Hospitals. She died one month following operation with the complications of pylephlebitis and liver abscesses. The writer has never observed this complication and has been unable to find any such reports in the literature. A brief recording of the salient features of this case therefore seems warranted.

On reflection it seems strange indeed that pylephlebitis and liver abscesses are not frequently a terminal event in patients succumbing to regional enteritis. Certainly the stage is all set for such a complication, namely, a diseased bowel wall which has been invaded to the point of perforation by all manner of intestinal bacteria, a thickened inflamed mesentery which on occasion contains actual abscesses and general debility predisposing to any overwhelming infection.

This unusual complication makes interesting speculation. Possibly its rarity is due to the fact that the infection is a chronic one in which the body has ample opportunity to throw up local barriers as well as to produce a certain amount of systemic immunity. Whatever the reason, it is not the purpose of this communication to attempt an answer.

CASE REPORT

F. S. (XL 80925) was a white American woman of thirty-seven who was first admitted to the University Hospitals in July, 1944. Her complaint was diarrhea of nine months' duration, epigastric cramps and nervousness. On this admission there were no positive findings except for a draining perirectal abscess. Laboratory findings were within normal range and no significant organisms were identified in stool cultures.

The second admission was in July, 1945, because of diarrhea, abdominal cramps, blood in the stool and a 40 pound weight loss since the onset of illness. Again findings were negative except for a low serum protein (5 Gm. per cent), a rectal fistula and occasional blood in the stool. X-ray study of the chest, esophagus, stomach, duodenum, terminal ileum and colon were negative. The patient improved on symptomatic care and was allowed to go home only to be admitted a third time one month later for excision of the rectal fistula. Pathologic study of this revealed only chronically inflamed granulation tissue. A second stage of the fistula operation was done on the fourth admission in November, 1945.

In December, 1946, the patient was admitted for the fifth time, still complaining of gas pains, diarrhea and occasional vomiting. Laboratory studies again were negative except for a moderate anemia. Further x-ray studies were made and these demonstrated a terminal ulcerative ileitis and probably ulcerative colitis. Attempts were made to improve the patient's physical condition by means of diet and transfusions. This was partially successful. Sulfasuxidine was started one week prior to contemplated surgery. Complete intestinal obstruction was never a threat in this woman although at times she became moderately distended.

On January 31, 1947, the abdomen was explored through a right lower rectus incision. The terminal 2 feet of ileum presented the typical picture of the acute phase of regional

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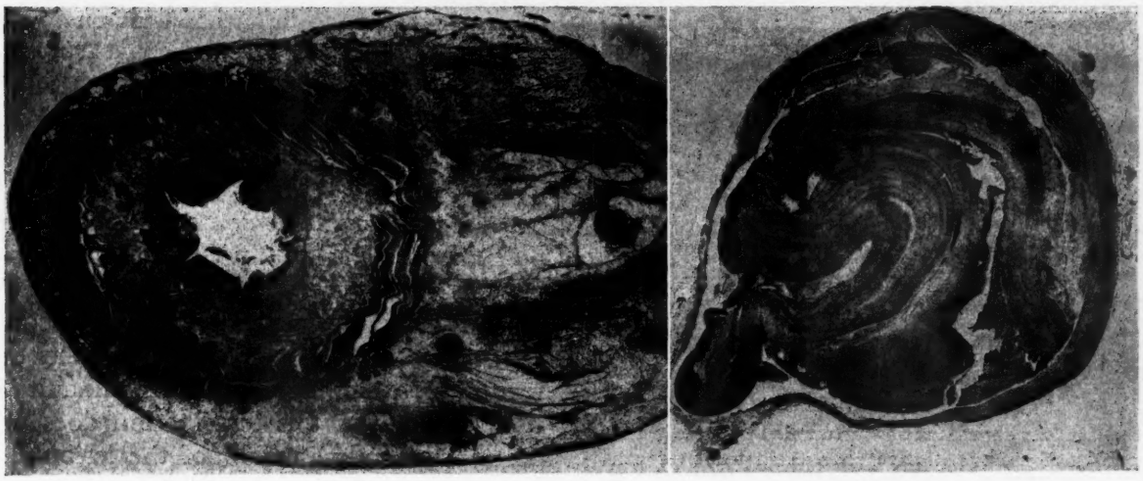

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FIG. 1. Fibrosis and edema of terminal ileum and its mesentery; small thrombosed veins can be seen; numerous minute abscesses were found toward the base of the mesentery (not shown in cut). The dark group of cells to the right is hyperplastic lymphoid tissue.

FIG. 2. Portal vein completely blocked with thrombus. In the vein wall there are areas of inflammatory cell infiltration and actual suppuration.

enteritis. The gut wall was greatly thickened by a brawny edema. The rope-like portion of the bowel seemed to have practically no lumen. Its supporting mesentery was very thick, edematous and shortened. The disease stopped abruptly at the cecum and no abnormalities were noted in the ascending or transverse colon. Proximally the disease gradually decreased in intensity until the ileum appeared normal at a distance of 3 feet from the cecum. At this point the ileum was joined to the transverse colon by a simple side-to-side anastomosis, giving a 1½ inch stoma. This was done in an anti-peristaltic direction and without dividing the distal ileum to exclude it from the circuit. Because of the patient's rather critical condition no thought was given to the possibility of a resection of the diseased gut. A lymph node removed from the mesentery of the ileum demonstrated only hyperplasia and chronic inflammation.

The postoperative course was exceptionally smooth with considerable improvement in abdominal pain and discomfort. Moderate diarrhea continued. The patient showed steady progress so that she was discharged on the twentieth postoperative day (February 20, 1947), in fair physical condition.

Six days later this patient returned complaining of vomiting and recurrence of severe diarrhea. She appeared quite ill, with a temperature of 102°F. The white blood count was 17,500 with 91 per cent polymorphonuclears; the urine was loaded with pus cells. There was slight diffuse abdominal tenderness and distention. Lacking a definite diagnosis the patient was treated symptomatically with transfusions and intravenous fluids as indicated by blood findings. Her course was progressively downhill. She became comatose on the second day after admission and a definite icteric tint to the skin became apparent two days later. The jaundice deepened and numerous petechial hemorrhages were noted about the neck. Penicillin and sulfadiazine were given emperically with clearing of the urinary tract infection and lowering of the temperature to 99° to 100°F. The patient, however, became more comatose, dyspneic and jaundiced.

She died March 6, 1947, with an elevated total non-protein nitrogen, dependent edema and edema of lungs with pleural effusion. Death occurred thirty-four days after operation and fourteen days after she was thought to have made a satisfactory postoperative convalescence and was discharged from the hospital.

At autopsy (L2094) the condensed, pertinent findings were as follows: The abdomen contained approximately 1,500 cc. of clear bile-stained fluid. The ileotransverse colostomy was well healed with an ample stoma. Fibrosis and edema of the terminal ileum showed no change over that seen at operation. (Fig. 1.) Microscopically, numerous abscesses were demonstrated in the thickened mesentery of the ileum. Also noted were mesenteric veins containing thrombi. These thrombi could be traced upward

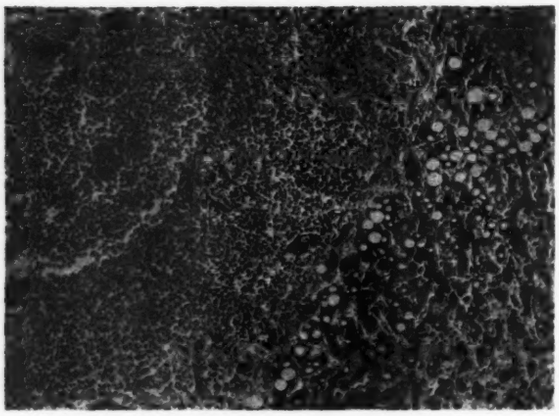

FIG. 3. Liver abscess; pus is surrounded by loose granulation tissue. Degenerative changes in the liver cells on the right are representative of those found throughout this organ.

through the superior mesenteric vein into the portal vein. Here microscopic sections demonstrated a suppurative pylephlebitis. (Fig. 2.)

The liver was yellowish brown and weighed 2,150 Gm. The cut section demonstrated many small abscesses containing a watery, gray pus. (Fig. 3.) From one or more of these hepatic abscesses pus had burrowed inside the falciform ligament, down to the anterior abdominal wall. Culture of the pus revealed a variety of organisms. (E. coli, non-hemolytic streptococcus, diphtheroids). These, of course, were secondary invaders forming an ascending infection from the gut to the liver. Ulcerations were present in the mucosa of the ileum. Undoubtedly the bacteria gained access to the venous channels by this route. Why the tissue invasion should have occurred in this particular manner was not explained by the postmortem examination.

The lungs demonstrated a rather extensive terminal hypostatic bronchopneumonia. The kidneys were normal except for mild tubular degeneration. Other organs including the brain were not remarkable.

SUMMARY

A case of regional enteritis ending in pylephlebitis and multiple liver abscesses is here briefly recorded.

The writer has never seen such a complication and has been unable to find the record of a similar case. It is difficult to understand why this termination does not occur frequently in view of the lesion site and its potentialities. It is suggested that one reason for this rarity may be that the disease is fundamentally a chronic one allowing local tissue barriers as well as systemic immunity to play an important rôle.

Just when the pylephlebitis and the liver abscesses appeared in this case cannot be accurately determined from the patient's course or from the pathologic sections. It seems possible that the operative trauma was sufficient to initiate the terminal event. Since abscesses were demonstrated in the mesentery at the postmortem examination, it seems possible that these may have broken through their natural confines during the final operation, giving rise to liver abscesses. The liver abscesses on tissue section appeared to be at least several weeks old. The thrombosis of the portal vein, of course, was a terminal episode.

Hemophilia in Twins*

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THE occurrence of hemophilia in twins is of special genetic interest. The appearance of the disease in one or both twins has been observed by various investigators who have gathered statistics on hemophilic families. Skold[1] in his study of sixty affected families in Sweden found four sets of twins in two of which the disease occurred in both boys. The author does not state whether these were identical (enzygotic) or fraternal (dizygotic). In a third set the boy was a bleeder while his sister was normal, but the potentiality of being a carrier remained undetermined. The fourth twins were girls both of whom were carriers since each had hemophilic offsprings. Again no mention is made whether they were enzygotic. Birch[2] in her series of seventy-five hemophilic families found three sets of twins. In one the boy was a bleeder and the sister normal, with the possibility of being a carrier. In another set one boy was normal while the twin brother was a severe bleeder who died of internal hemorrhage in early childhood. The third twins in the series were identical or enzygotic. Both had the same blood grouping and ran similar clinical courses.

It is logical to expect that in identical twins both should inherit the defect. The following case history is therefore not only interesting but also mystifying.

CASE REPORT

A normal mother with a negative family history of bleeding gave birth to twins, D. S. and T. S., March 31, 1942. The two boys were very similar in appearance and the mother remembers being told that there was only one placenta. Unfortunately this was not recorded on the hospital chart. Both boys were circumcised when a week old. T. S. had no abnormal bleeding and left the hospital with his mother two days later. D. S. had severe bleeding following the operation and required a transfusion of 75 cc. of fresh blood before the hemorrhage was controlled. The coagulation time (procedure not specified) was two and one-half minutes.

Up to the age of three, D. S. had no serious hemorrhages, but it was observed that he bruised easily and developed marked swelling from trivial bumps. His brother (T. S.) at no time showed any bleeding tendency. When he was three years old, D. S. was studied by Dr. Frederick Madison and one of us (A. J. Q.) on March, 1945. The following findings were obtained:

Red blood cells	4,160,000	Clotting time of recalcified plasma (3)	
White blood cells	6,800	After low centrifugation	—210 sec.
Hemoglobin	12 Gm.	After high centrifugation	—225 sec.
Platelets	112,000	Prothrombin (100%)	12 sec.
Bleeding time	3 min.	Ascorbic acid	—2 mg. per 100 cc. of blood
Coagulation time (Lee-White)	5 min.	Clot retraction	—within 1 hr.

These results were inconclusive and did not permit a definite diagnosis of hemophilia; but two months later when a definite hemorrhagic episode occurred with bleeding into his groin and left thigh, positive findings were obtained:

Coagulation time (Lee-White)	10½	min
Coagulation time of recalcified plasma		
After low centrifugation	180	sec.
After high centrifugation	360	sec.
Prothrombin (100%)	12	sec.

From then on his clinical course has been typical of hemophilia. At one time he bled profusely from a small cut on his tongue. At another time he had a hemorrhage into his right knee. He has never had nose bleeds, an observation

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which is not surprising since many hemophilics never have epistaxis.

His bleeding episodes appear to be cyclic and often are initiated by prodromal manifestations. This is particularly well illustrated by the following incident: For no accountable reason he suddenly began to feel listless and complained of being unusually tired. Following this he lost his appetite and two days later began vomiting and complained of pain in the abdomen with localization over McBurney's point. This necessitated making a diagnosis of acute appendicitis although the possibility of abdominal hemorrhage was recognized. The decision to operate was made. He was given 300 cc. of lyophilized plasma intravenously. The transfusion was started an hour before the operation and completed during the operation. The appendix was found normal but there was a retroperitoneal hemorrhage behind the cecum. The appendix was removed and special care was taken to tie off all bleeders. No unusual bleeding was encountered. The administration of plasma definitely improved the hemostatic property of his blood as shown by the prothrombin consumption test.[4,*] The time was eleven seconds before the transfusion and twenty-one seconds after he received the plasma. Two and one-half days after the operation it was still twenty-one seconds and the coagulation time (Lee-White) seven and one-half minutes. Twenty-four hours later, however, the prothrombin consumption time was eleven seconds and he was bleeding into his incision. He was given 250 cc. of fresh blood. The prothrombin consumption time immediately increased to twenty-five seconds, hemorrhage was controlled and he had no further bleeding.

He had another unusual bleeding episode. As the result of a cold he developed a severe cough. Apparently from strain he ruptured a small vessel in the anterior neck and bled into the mediastinum; this was verified by roentgenologic examination. He was given a transfusion of 250 cc. fresh whole blood. The prothrombin consumption time before the transfusion was ten and one-half seconds and sixteen and one-half seconds after the blood was given.

While D. S. is a typical hemophiliac, his twin brother is entirely normal. There is evidence that they are identical twins. Some of the similarities are:

	D. S.	T. S.
Eyes	Hazel brown	Hazel brown
Nose and ears	Same shape and size (including type of ear lobe)	
Hair	Very dark brown	Very dark brown
	Same type whorl and identically located	
Height	48½ in.	47¼ in.
Weight	48 lb.	46 lb.
Blood grouping	A_1 MN Rho′	A_1 MN Rho′*
Probable genetic pattern	CDe/CDe	CDe/CDe
Mothers blood grouping—BM Rho′	(CDe/CDe)	

* We are indebted to Dr. Tibor J. Greenwalt and the Junior League Blood Center of Milwaukee for these studies.

The coagulation studies of the family were:

	D. S.	T. S.	Father	Mother	
Coagulation time (Lee-White)	13½	5½	6	5	min.
Coagulation time of recalcified plasma					
After high centrifugation	600	135	...	..	sec.
After low centrifugation	210	105	...	..	sec.
Prothrombin time	12½	12½	12½	12½	sec.
Prothrombin consumption time					
After 1 hr	11	19	20	18	sec.
After 4 hr	12	23	25	23	sec.

After mixing 1 cc. of D. S. blood with 1 cc. of his brother's a coagulation time of six minutes resulted and the prothrombin consumption time was twenty seconds in one hour.

COMMENT

From the data presented it is clear that one twin is a typical hemophiliac whereas his brother is entirely normal. All the evidence obtainable strongly indicates that these boys are identical twins. Their blood types are exactly the same. They are very similar in appearance. (Fig. 1.) The hemophilic boy is a little taller and heavier which his mother attributes to the greater

* The prothrombin consumption test consists in allowing blood to coagulate and then determining the prothrombin remaining unconverted in the serum. The test is carried out as follows: 0.1 cc. of human oxalated plasma treated with calcium phosphate (which serves as the source of fibrinogen) is mixed with 0.1 cc. of thromboplastin and 0.1 cc. of 0.02 M calcium chloride. To this mixture, 0.1 cc. of serum is rapidly added from a pipette and the formation of a clot accurately timed. Normal blood has a prothrombin consumption time of sixteen to thirty-five seconds, whereas hemophilic plasma has a value varying from nine to twelve seconds.

amount of rest he receives. The color of the eyes and the shade of their hair are identical and even such details as the type and location of the whorl of their hair completely match. There is a similarity of their finger prints, but these have not been studied thoroughly. If it were not for the finding that one is a bleeder and the other normal, one would unhesitatingly classify them as enzygotic. Assuming that they are identical twins, one is at a loss to explain how one has the characteristic defect of true hemophilia while the other escaped this inborn error in the blood.

Since the family history as far as it is obtainable is negative, the simplest explanation would be to postulate a mutation in the affected twin and class him as a sporadic hemophiliac. But one must be extremely cautious in calling any case sporadic in view of the insidious heredity pattern of the disease. If it were common for this disease to originate *de novo*, one would expect an incidence in the negro approximating that of the white race. Yet it is doubtful whether true hemophilia has ever been unequivocally demonstrated in a person of pure negro ancestry. It must be emphasized that the diagnosis of hemophilia was never conclusive until the development of recent methods particularly the prothrombin consumption test, and that acquired hemophilia-like disease[5,6] and the hereditary types of congenital hypoprothrombinemia[7] closely resemble true hemophilia clinically, and are also characterized by a prolonged coagulation time.

In view of these considerations no attempt will be made to explain the paradoxical occurrence of hemophilia in only one of presumably identical twins. The purpose of this paper is merely to present this unusual observation, since with the accumulation of such diverse findings more light may be shed on the peculiarities of inheritance.

SUMMARY

The history, clinical and laboratory findings are presented of a hemophilic boy who is one of presumably identical twins. His brother is entirely normal.

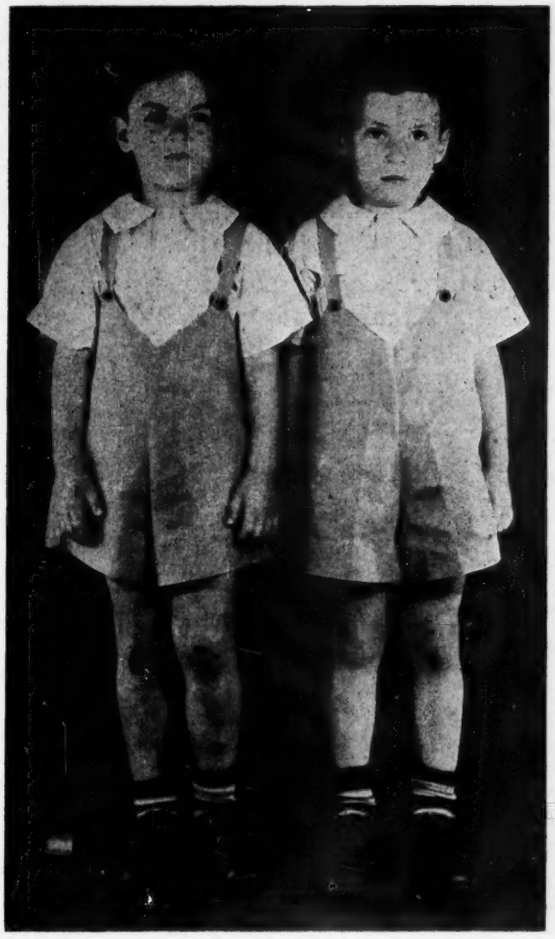

FIG. 1. D. S., the hemophilic twin, is on the left. Due to hematomas, particularly of the forehead, and scarring about the mouth, the facial features have been somewhat changed. Consequently the similarity in appearance of D. S. and T. S. is not as striking as is often observed in identical twins.

REFERENCES

1. SKOLD, E. On hemophilia in Sweden and its treatment by blood transfusion. *Acta med. Scandinav.*, 150: 247, 1944.
2. BIRCH, C. L. Hemophilia: Clinical and Genetic Aspects. Illinois Medical and Dental Monograph, No. 4, University of Illinois, 1937.
3. QUICK, A. J. The diagnosis of hemophilia. *Am. J. M. Sc.*, 190: 469–474, 1935.
4. QUICK, A. J. Studies on the enigma of the hemostatic dysfunction of hemophilia. *Am. J. M. Sc.*, 214: 272–280, 1947.
5. MADISON, F. W. and QUICK, A. J. Hemophilia-like disease in the female. With a note on the clotting time of recalcified plasma. *Am. J. M. Sc.*, 209: 443–447, 1945.
6. QUICK, A. J. and STEFANINI, M. Activation of plasma thromboplastinogen and evidence of an inhibitor. *Proc. Soc. Exper. Biol. & Med.*, 67: 111–112, 1948.
7. QUICK, A. J. Congenital hypoprothrombinemia and pseudo-hypoprothrombinemia. *Lancet*, 2: 379, 1947.

Book Reviews

The Parathyroid Glands and Metabolic Bone Disease. Selected Studies. By Fuller Albright, M.D. and Edward C. Reifenstein, Jr., M.D. 393 pages. Baltimore, 1948. The Williams and Wilkins Company. *Price* $8.00.

New publications of Fuller Albright and his associates at the Massachusetts General Hospital are always received with interest; this concise, authoritative monograph summarizes the group's major contributions to the field of calcium and phosphorus metabolism during the past two decades.

Although emphasis is given to hyperparathyroidism, osteoporosis and osteomalacia, considerable information about other diseases of bone is included. The discursive style makes pleasant reading, the numerous illustrations are well chosen and the twenty-page bibliography covers most of the relevant literature.

The chapter on physiology is short but adequate. Without embarking upon extended technical discussions, the authors review the available evidence dealing with the action of the parathyroid glands and the formation and maintenance of bone. It is evident here, as stated in the preface, that their "hypotheses . . . are subject to change without notice." Although the authors' theories of parathormone action have been modified to include a direct action on bone, the recent work of Jahan and Pitts and of Stoerk may require that further modification be made in the next edition.

A few theoretical inconsistencies appear in the monograph; attention should be called to at least one of these: The dangers of metastatic calcification in chronic renal insufficiency are emphasized in the section on "parathyroid poisoning"; some paragraphs later, however, treatment with alkali, vitamin D and a high calcium intake is recommended for the bone disease sometimes accompanying this disorder. Although the resulting increase in calcium absorption from the intestinal tract may produce "spectacular" improvement in the osteitis fibrosa generalisata, progressive renal damage would seem inescapable.

In the same chapter acidosis is held to be the cause of the bone disturbance in secondary hyperparathyroidism; the relation of acidosis occurring in renal tubular disease without nitrogen retention to the associated osteomalacia is, however, not mentioned in the discussion of this disease. There is little question that the authors' conception of the pathogenesis of the bone disorder accompanying renal tubular acidosis will require some modification as new evidence is obtained. The value of their contribution to the treatment of this disorder, however, remains undisputed.

There are few publications in the field of bone disease in which as much fundamental information is so authoritatively presented and applied to clinical problems in so brief a space as in this monograph. It will be of interest to the practicing physician as well as to the student of bone disease.

K.I.P.

Communicable Disease Control. By Gaylor W. Anderson, and Margaret G. Arnstein, M.D., 2nd ed., 450 pages. New York. The Macmillan Co. *Price* $5.00.

This second edition of an introductory reference book of preventive medicine brings to the reader an up-to-date account of the available control measures in the realm of communicable diseases. As is emphasized by the authors the material is primarily concerned with community protection rather than with the handling of individual patients with infectious diseases.

The first part of the book briefly covers the regulations and responsibilities of the various local, state and federal agencies, while the remaining sections evaluate the different control measures available in specific communicable diseases.

For general public health purposes the subject is covered in great enough detail. For those wishing to pursue particular problems in greater detail the authors have included adequate references at the conclusion of each chapter.

A.R.L., JR.

AUTHOR INDEX VOLUME VII

SUBJECT INDEX VOLUME VII

(E.) = Editorial

The American Journal of Medicine

Volume VII

JULY TO DECEMBER

1949

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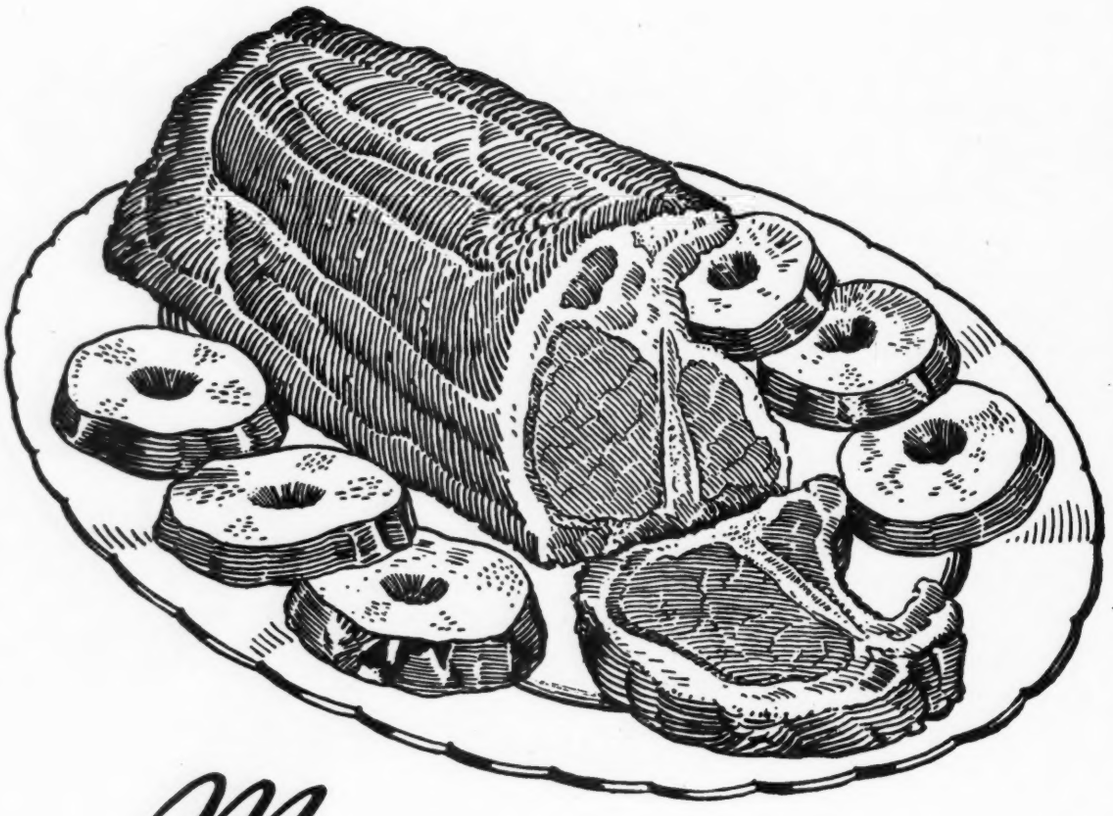

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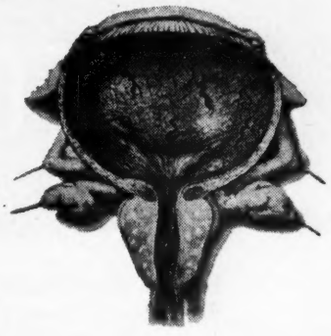

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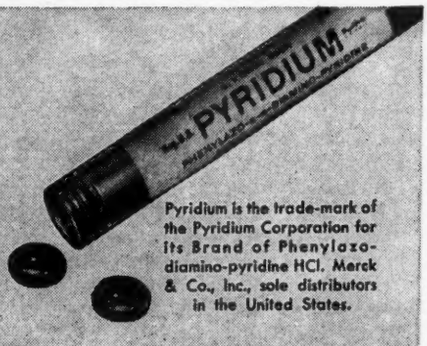

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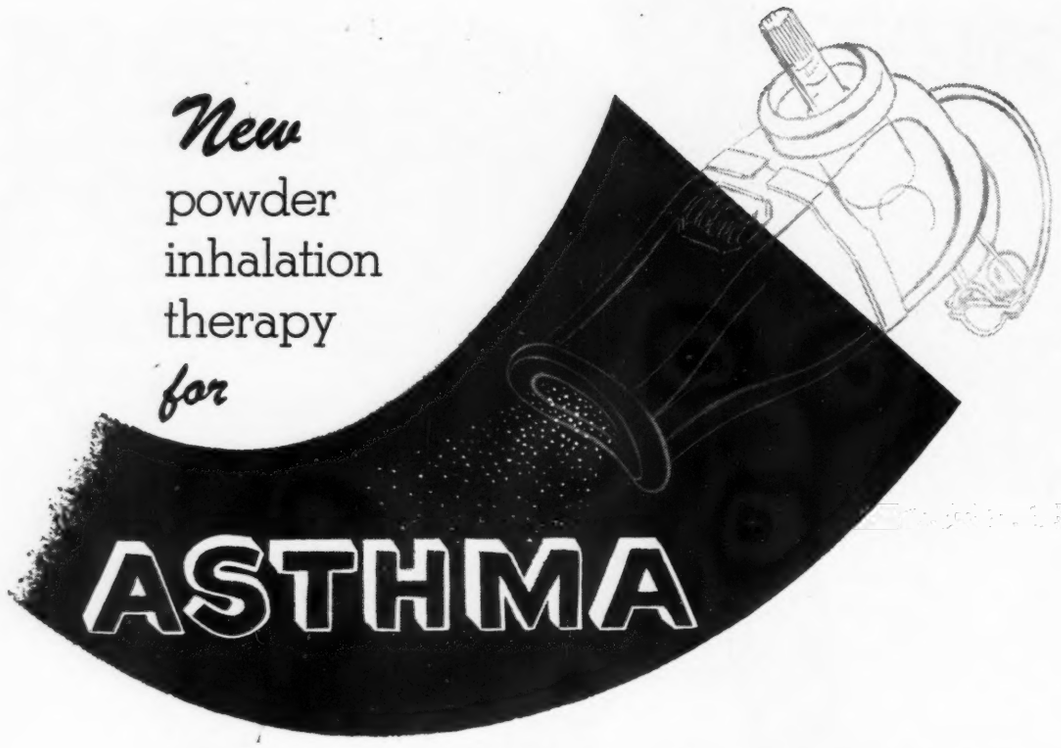

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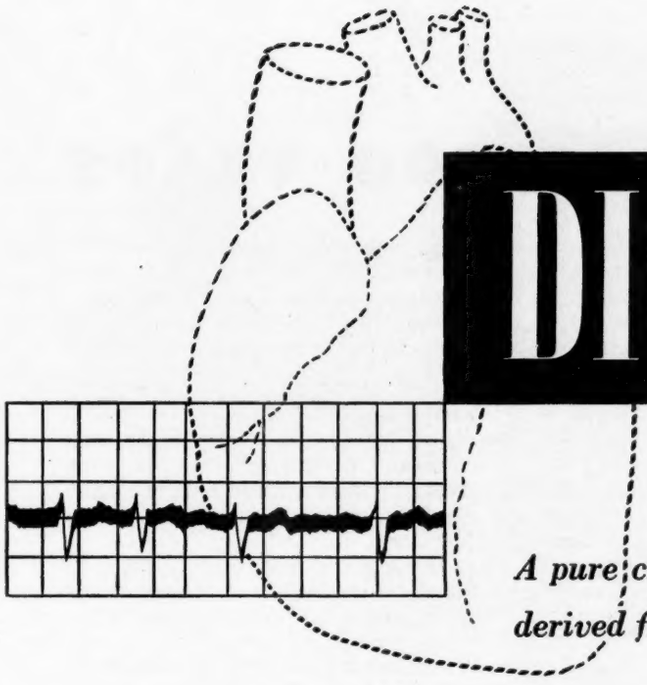

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1. Harvey, R.M.; Ferrer, M.I.; Cathcart, R.T.; Richards, D.W., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Am. J. Med. 7:439 (Oct.) 1949.

2. Batterman, R.G., and DeGraff, A.C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure: Am. Heart J. *34*:663 (Nov.)1947.

3. Schaaf, R.S.; Hurst, J.W., and Williams, C.: The Management of Auricular Flutter: Med. Clin. N. Am. p. 1255 (Sept.) 1949.

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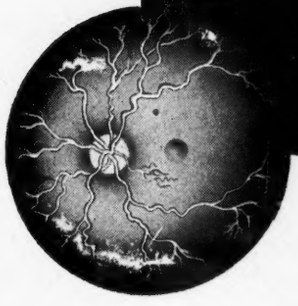

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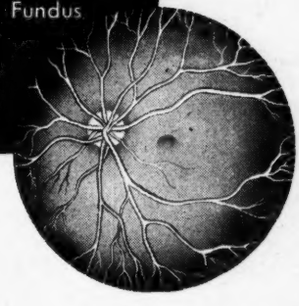

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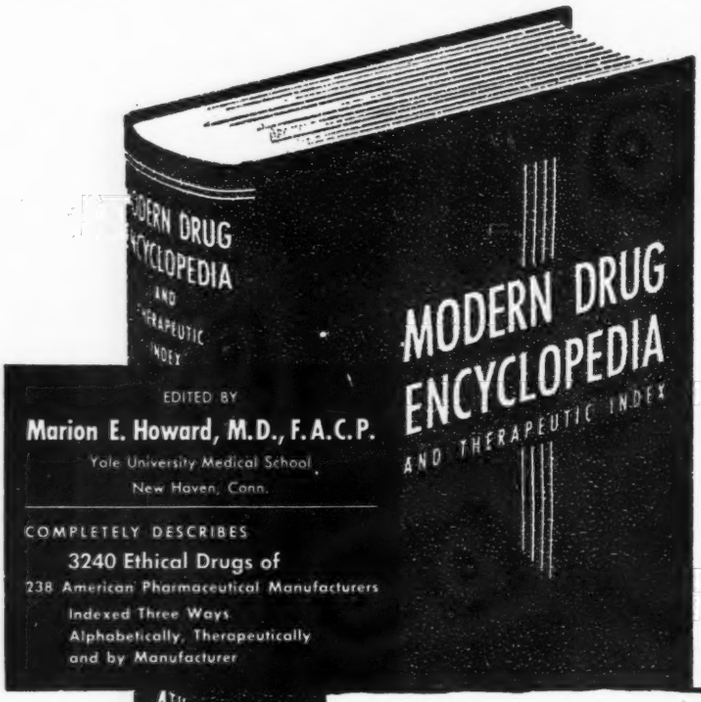

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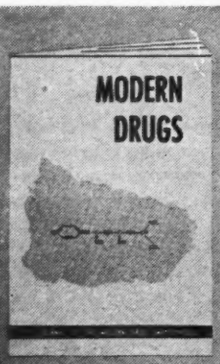

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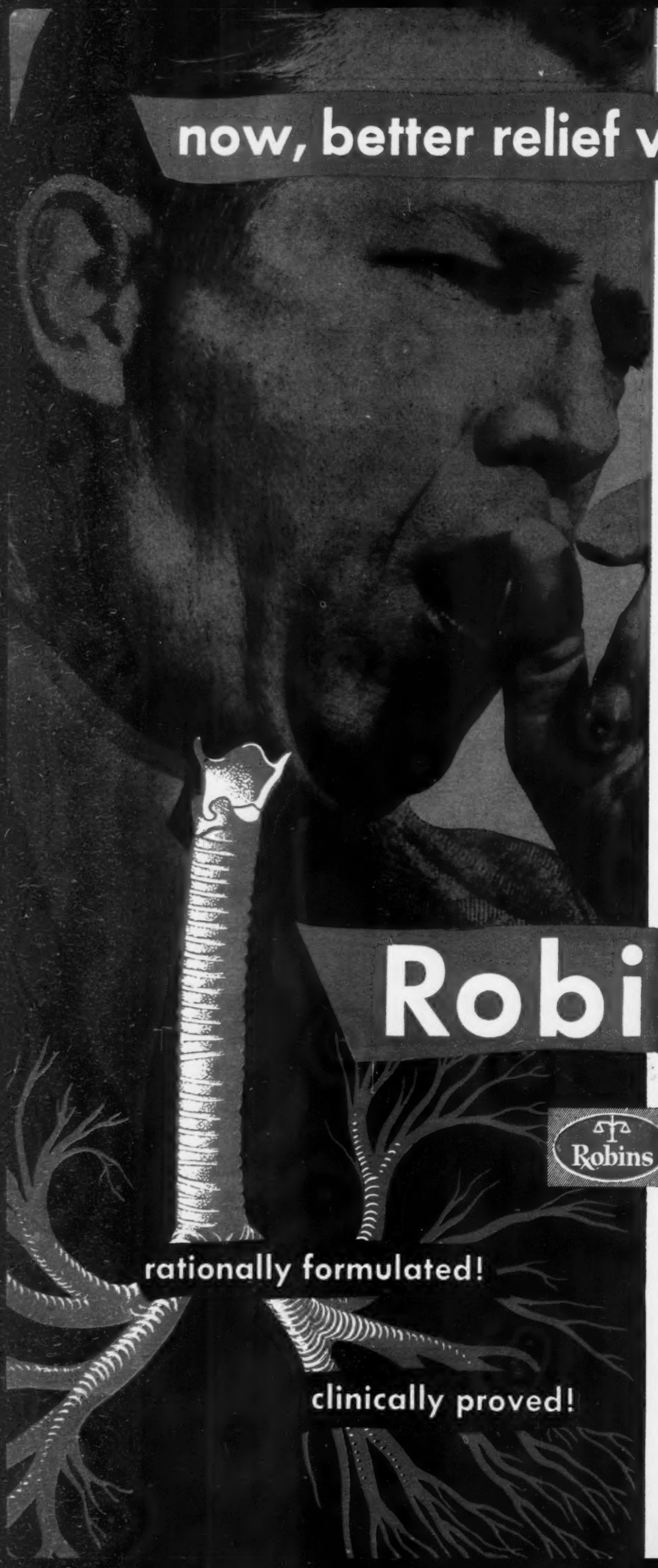

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DOSAGE: Children: one-half to one teaspoonful, according to age, three or more times daily. Adults: one or two teaspoonfuls, as necessary every two to three hours.

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REFERENCES: 1. Connell, W. F. et al: Canadian Med. Assoc. J., 42:220, 1940. 2. Perry, W. F. and Boyd, E. M.: J. Pharm. Exper. Ther., 73:65, 1941. 3. Stevens, M. E. et al: Canadian Med. Assoc. J., 48:124, 1943. 4. Foltz, E. E. et al: J. Lab. Clin. Med., 28:603, 1943. 5. Graham, B. E.: Ind. Eng. Chem., Ind. Ed., 37:149, 1945. 6. Schulz, F. and Deckner, S.: Klin. Wochschr., 21:674, 1942.

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1. Lisser, H.: Calif. & West. Med. 64: 177, 1946

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